Preparation, Characterization and Applications of Macrocycle-Dendrimer Conjugates

by
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DECLARATION

By submitting this thesis electronically, I declare that the entirety of the work contained therein is my own, original work and that all sources I have used or quoted have been acknowledged by means of complete references.

August 2013

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CONFERENCE CONTRIBUTIONS

Poster presentations

D. Wilbers, S.F. Mapolie, R.C. Luckay

The synthesis and characterization of macrocycles immobilized on the periphery of dendrimers. CATSA annual conference at Muldersdrift 2011

The synthesis and characterization of macrocycles immobilized on the periphery of dendrimers. CATSA annual conference at Club Mykonos, Langebaan 2012

ABSTRACT

In this thesis we describe various attempts at incorporating macrocycles into dendritic architectures to form macrocycle-dendrimer conjugates with the aim of preparing materials that would exhibit properties that are more than the sum of the constituent parts, in this case macrocycles and dendrimers. A further aim was the synthesis and characterization of metallodendrimers based on such scaffolds and to test these as catalyst precursors in the catalytic oxidation of alcohols.

The synthesis of two different types of conjugate systems was attempted; *viz*. dendrimers functionalized with macrocycles on the peripheries and dendrimers with macrocyclic cores.

The synthesis of conjugate systems based on cyclam as the macrocycle was attempted. This required the mono functionalization of cyclam with a linker molecule capable of further reaction with the functional groups at the periphery of commercially available N,N,N,N-tetrakis(3-aminopropyl)-1,4-butanediamine dendrimer. Several approaches were taken in trying to make such conjugate systems but they were not entirely successful. One of the major issues was the final deprotection step, of the Boc-protected cyclam units which proved difficult in our hands.

Another approach to prepare the target conjugates involved the use of click chemistry in order to synthesize a dendrimer with an aromatic core and cyclam peripheries. A dendrimer with Boc-protected cyclam peripheries that are bonded through triazole groups to the aromatic core was synthesized. However, subsequent attempts at de-protection of the cyclam functionalities of this conjugate failed to yield the pure de-protected dendrimer.

Greater success was achieved with the preparation of a dendrimer with a macrocyclic core. A cyclam cored dendrimer with salicylaldimine peripheries was successfully synthesized and characterized. This dendritic ligand was complexed to Cu(II), Ni(II) and Zn(II) metal ions respectively to form a series of new metallodendrimers. These metallodendrimers were fully characterized using a range

of analytical techniques including FT-IR spectroscopy, mass spectrometry, elemental analysis, thermogravimetric analysis, magnetic susceptibility measurements and NMR spectroscopy where appropriate.

The Cu(II) and Ni(II) metallodendrimers were tested as catalyst precursors in the catalytic oxidation of benzyl alcohol to benzaldehyde. The catalytic system consisted of the appropriate metallodendrimer, the free radical, 2,2,6,6-tetramethylpiperidinyl-1-oxyl (TEMPO) and O_2 as the oxidant. The reaction parameters, namely the nature of the solvent, catalyst loading, substrate concentration and reaction temperature were sequentially optimized to achieve the best catalytic efficiency. The Cu(II) catalyst precursor exhibited relatively high catalytic activity and achieved TOF's between 40 and 30 when operating under the optimized conditions, while the Ni(II) catalytic system showed very poor catalytic activity.

OPSOMMING

In hierdie tesis beskryf ons pogings om makroringe in die dendritiese argitektuur te inkorporeer om makroring-dendrimeer gekonjugeerdes te vorm met die hoop dat sulke molekules eienskappe sal toon wat meer is as die somtotaal van die afsonderlike eenhede. ‘n Verdere doel was die sintese en karakterisering van metallodendrimere gebaseer op sulke draers sowel as die toetsing van hierdie molekules as pre-katalisore in die katalitiese oksidasie van alkohole.

Pogings tot die sintese van twee verskillende tipes makroring-dendrimeer gekonjugeerdes word beskryf naamlik, dendritiese ligande met makroringe by die buiterand sowel as dendritiese ligande met ‘n makroring as kern word bespreek.

Die sintese van makroring-dendrimeer gekonjugeerdes gebasseer op die makroring cyclam word beskryf. Hierdie sintese vereis die gebruik van ‘n mono-gefunksioneerde cyclam wat ‘n gepaste koppelingsgroep besit. Hierdie koppelingsgroep kan dan verder met funksionele groepe op die oppervlak van die kommersieel beskikbare DAB-dendrimeer reageer. Verskeie pogings is aangewend om sulke gekonjugeerde stelsels te sintetiseer maar hierdie pogings was nie volkome suksesvol nie. ‘n Groot uitdaging was die gebruik en gevolglike latere verwydering van beskermende groepe soos Boc.

‘n Ander benadering het gebruik gemaak van “click” chemie met die doel om ‘n dendrimeer bestaande uit ‘n aromatiese kern en cyclam periferie te vorm. ‘n Dendrimeer met Boc beskermde cyclam eenhede op die buiterand geheg aan ‘n aromatiese kern deur triasool groepe is gesintetiseer. Die verwydering van die beskermende groepe geheg aan die cyclam eenhede was egter weereens ‘n probleem en hierdie metode kon nie die suiwer dendrimeer lewer nie.

Groter sukses is behaal met die sintese van ‘n dendrimeer met ‘n cyclam kern en salisielaldimien periferieë. Die dendritiese ligand is vervolgens met metaalsoute van Cu(II), Ni(II) en Zn(II) gereageer om verskeie multikern metaalkomplekse te vorm. Die metaalkomplekse is volledig gekarakteriseer deur verskeie analitiese tegnieke

insluitende infrarooi spektroskopie, massa spektrometrie, termografiese analiese, mikroanaliese asook KMR spektroskopie waar moontlik.

Die Cu(II) en Ni(II) metaalkomplekse is geëvalueer as pre-katalisatore in die katalitiese oksidasie van alkohole. Hierdie katalitiese sisteem bestaan uit die metaalkompleks, die radikaal TEMPO en molekulêre suurstof. Die invloed van verskeie reaksie- parameters soos die tipe oplosmiddel, die hoeveelheid katalisator, die konsentrasie van die alkohol asook die temperatuur is ondersoek. Gevolglik is die optimale kondisies bepaal om die hoogste opbrengs van bensaldehied te lewer. Die Cu(II) kompleks het ‘n relatief hoë omset van bensielalkohol na bensaldehied getoon met omset frekwensie waardes tussen 30 en 40 onder die optimale kondisies. Die Ni(II) kompleks het egter swak aktiwiteit getoon vir hierdie transformasie.

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LIST OF ABBREVIATIONS AND SYMBOLS

°	Degrees
°C	Degrees Celsius
µm	Micrometre
AIDS	Acquired immunodeficiency syndrome
Atm	Atmosphere
ATR	Attenuated total reflectance
Boc	tert-Butyloxycarbonyl
Br	Broad (broad signal in NMR spectroscopy)
BM	Bohr Magneton
Calc.	Calculated
cm^{-1}	Wavenumber (inverse centimetre)
Cyclam	1,4,8,11-tetraazacyclotetradecane
d	Doublet (in NMR spectroscopy)
DAB	Diaminobutane
DCM	Dichloromethane
DEC	Decomposition
DENs	Dendrimer-encapsulated nanoparticles
DIBAL	Diisobutylaluminium hydride
DMF	Dimethyl formamide

DMSO	Dimethyl sulfoxide
E.A.	Elemental analysis
EPR	Electron paramagnetic resonance
et al	And others
ESI	Electrospray ionization
Et_3N	Triethylamine
EtOAc	Ethyl acetate
FT-IR	Fourier transform infrared (spectroscopy)
g	gram
G_x	Dendrimer Generation, where x= 0,1,2,3…
GC	Gas chromatography
GPC	Gel permeation chromatography
HIV	Human immunodeficiency virus
HPLC	High-performance liquid chromatography
HPNPP	2-hydoxypropyl-p-nitrophenyl phosphate
Hz	Hertz
IUPAC	International Union of Pure and Applied Chemistry
M	Molar concentration
m/z	Mass to charge ratio
M.p.	Melting point
MeCN	Acetonitrile
MeOH	Methanol
MHz	Megahertz

mg	Milligram
ml	milliliter
MLCT	Metal to ligand charge transfer
mol	Mole
mmol	Millimole
M.S.	Mass spectrometry
nm	nanometre
NMR	Nuclear magnetic resonance
PAMAM	Poly(amidoamine)
pKa	Symbol for acid dissociation constant
PPI	poly(propylene imine)
PPM	Parts per million
Q	Quartet (In NMR spectroscopy)
RNA	Ribonucleic acid
S	Singlet
T	Triplet (in NMR spectroscopy)
TACN	1,4,7-triazacyclononane
TEMPO	(2,2,6,6-Tetramethylpiperidin-1-yl)oxyl
TEMPOH	Protonated TEMPO
TFA	Trifluoroacetic acid
TfOH	Trifluoromethanesulfonic acid
TGA	Thermogravimetric analysis
THF	Tetrahydrofuran

TLC	Thin layer chromatography
TOF	Turnover frequency
TON	Turnover number
TsOH	*p*-Toluenesulfonic acid
UV-Vis	Ultraviolet–visible spectroscopy

CHAPTER 1: A LITERATURE REVIEW OF DENDRIMERS, MACROCYCLES AND THEIR APPLICATIONS

1.1 Introduction

Macrocycles and dendrimers are two types of compounds that are currently of great research interest. Macrocycles form very stable complexes with many transition metal ions and have shown to be promising in many biological applications while dendrimers are particularly attractive supports for transition metal complexes, or metal nanoparticles in the field of catalysis. In this chapter the history of dendrimers as well as the synthesis of dendritic materials and finally the most important applications of dendrimers is reviewed. Following this, we briefly discuss some background information on macrocycles. The history and synthesis of macrocyclic ligands as well as the origins of the macrocyclic effect is examined and the myriad of applications is discussed. Finally, reported examples of dendrimers bearing macrocycles (dendrimer macrocycle conjugates) at various points in the dendritic architecture and the potential advantages of these conjugate systems are highlighted. Based on the literature reviewed, the aims of this project are formulated.

1.2 Dendrimers

1.2.1 Overview of dendrimers

Dendrimers are defined as repetitively branched macromolecules. Dendrimers characteristically possess three important structural features and these are shown in Figure 1.1. These are the interior core, branching points that give rise to dendrimer generations and exterior peripheries. The dendrimer architecture of repetitive branching was first conceptualized by Flory in 1941. [1-3]

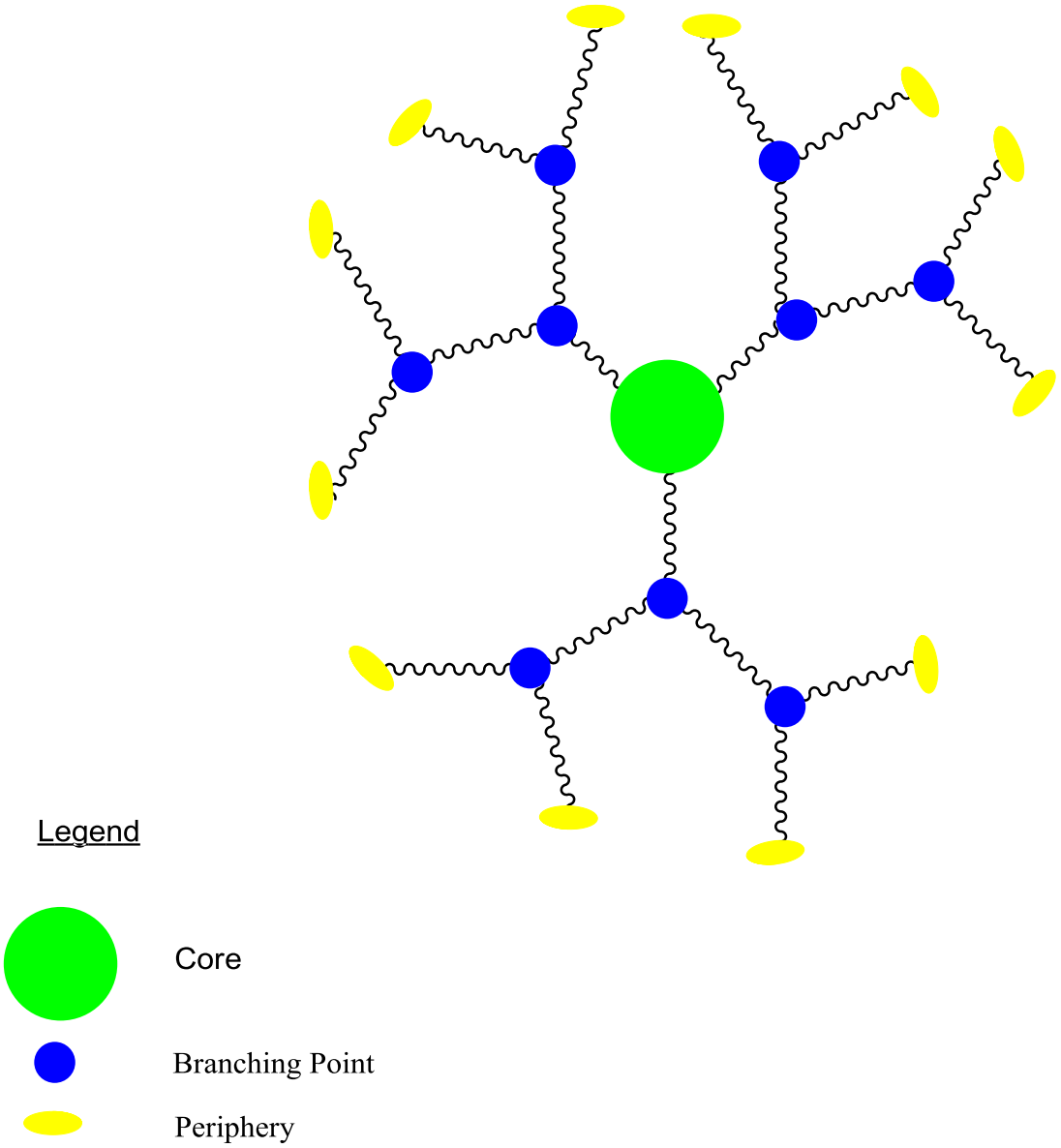


Figure 1.1: Typical dendrimer architecture

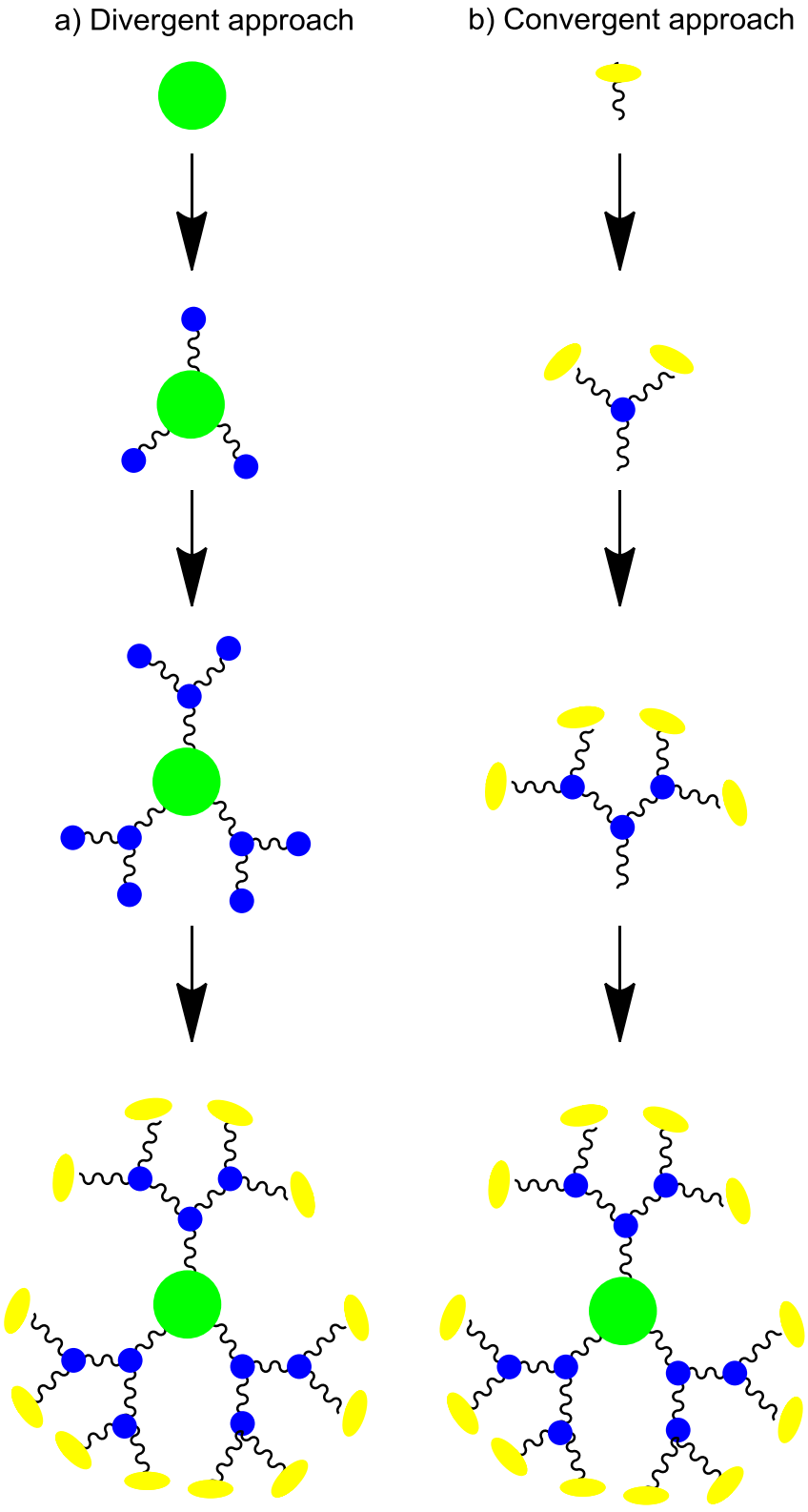
The first successful dendrimer synthesis however, was only reported in 1978 by Buhleier *et al.* who used the concept of repetitive branching in the synthesis of low molecular weight branched amines to create a new class of macromolecules that the authors named cascade molecules.[4] The Tomalia group at DOW Chemical Company independently developed and presented the divergent synthesis of dendrimers in 1984.[5] The term "dendrimer" first appeared in an article by the Tomalia group describing the synthesis of poly(amidoamine) dendrimers (PAMAM dendrimers) presented at the 1st International Polymer Conference in Japan.[5] The

article was subsequently published [6] in 1985 the same year as a communication by Newkome *et al.* that described the synthesis of arborols.[7] The terms “arborol” and “cascade molecule” are both synonymous with the term “dendrimer”, however, “dendrimer” is most often used in the literature.

1.2.2 Synthesis of dendrimers

The synthesis of dendrimers can be accomplished by two different methods namely the divergent method and the convergent method. These two different methodologies are depicted schematically in Scheme 1. The work of Vögtle *et al.* and Tomalia *et al.* introduced the divergent synthetic methodology.[4, 6] The divergent method starts with the synthesis of the interior dendrimer core. The dendrimer core possesses a specific number of reactive sites that are used to attach the dendritic branches. Dendrimer growth then continues outward to the periphery. The divergent approach is used commercially to produce the Starburst (trademarked) range of dendrimers by the DOW Chemical Co. This method has been employed for the production of very large dendrimers. One of the drawbacks of the divergent method is that it offers little control over the generation growth reaction. This can lead to incomplete dendrimer growth as well as side reactions. Another big problem with the divergent method is product separation. Incomplete dendrimers are difficult to separate from the target product. The phenomenon of incomplete dendrimer growth can also lead to low yields.

The convergent approach was developed between 1988 and 1989 and introduced by Fréchet *et. al*.[8] Convergent growth starts at what will become the periphery of the dendrimer instead of at the core. The synthesis of this dendron is then first completed before progressing inward towards the dendrimer core by coupling the dendron to the branching monomer at a reactive functional group. Convergent growth has several advantages when compared to divergent growth. Purification is often simplified by using convergent growth. Intermediate products in the overall synthesis of the dendrimer can be purified. The synthesized dendrons are usually purified before reaction with the branching monomer.



Scheme 1.1: The divergent (a) and convergent (b) synthetic methods

1.2.3 Properties of dendrimers

Increased research interest into dendrimers is fuelled by some unique properties of these macromolecules. The synthesis of dendrimers allows for very high structural conformity as the size and mass of synthesized dendrimers can usually be controlled, unlike the case for linear polymers, the synthesis of which often produces a range of different sized polymers. Due to the globular shape of dendrimers, internal cavities may be present within a dendrimer molecule. This can allow the dendrimer to encapsulate guest molecules or ions. Functional units can be placed either in the interior dendrimer core or on the periphery and this leads to different chemical and physical properties and thus behaviour of the materials.[9]

1.2.4 Applications of dendrimers

Since its discovery the applications of dendrimers have shown tremendous growth. Dendrimers are used in medicine and biological fields as well as in catalysis. The applications of dendrimers in these various fields are briefly reviewed below.

1.2.4.1 Medical field

Dendrimers can act as drug delivery agents and have been utilized to encapsulate and transport pharmaceutical molecules and metal salts. The low polydispersity of dendrimers also make these molecules ideal candidates for use as synthetic proteins. Dendrimer molecules are typically of uniform size due to the degree of control in the synthetic process compared to other polymers.

1.2.4.1.1 Encapsulation of biologically active materials

Many molecules that show promise as anticancer, anti-inflammatory and anti-microbial agents are sometimes not adopted by the pharmaceutical industry because of low bioavailability usually as a result of poor water solubility or poor cell membrane permeability. Certain dendrimers have been used in these cases because of their ability to cross cell membranes thus enhancing the bioavailability of these compounds. Figure 1.2 illustrates the two different methods of encapsulation. Encapsulation is done either through physical interactions with dendrimer molecules or through chemical bonding between the pharmaceutical and dendrimer. Often the dendrimer bound pharmaceutical is less toxic than the free molecule.[10]

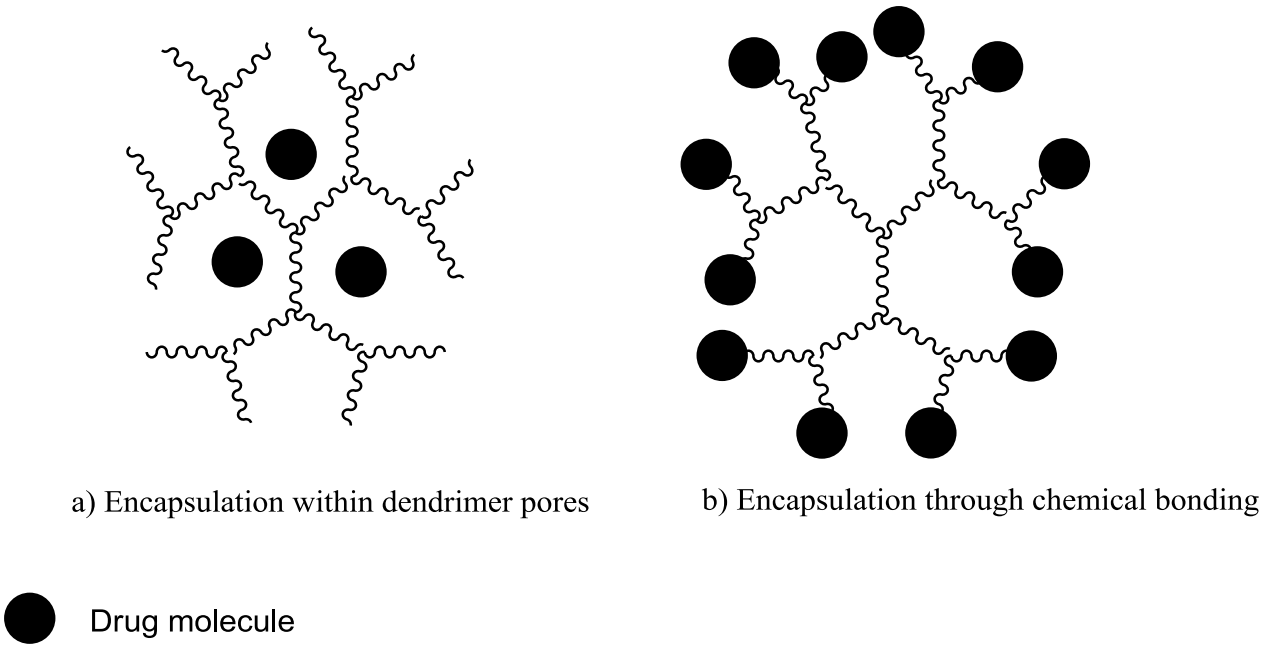


Figure 1.2: Drug encapsulation within pores (a) or throughchemical bonding (b)

The molecules 10-hydroxycamptothecin and 7-butyl-10-aminocamptothecin are used as anti-tumour compounds. The disadvantages associated with these compounds are their low water solubility and serious adverse effects in mammals such as inflammation of the bladder. These compounds were recently encapsulated in biocompatible dendrimers synthesized from glycerol and succinic acid.[11] The encapsulated pharmaceutical was then tested against four different human cancer cell lines. It was found that cells treated with the encapsulated pharmaceutical showed up to a 16-fold increased uptake of the camptothecin into the cells as well as better drug retention within the cells.[11]

The efficacy of the drug cisplatin is limited by its poor water solubility and low lipophilicity. Encapsulation of cisplatin within PAMAM dendrimers resulted in higher accumulation of the drug within tumour cells as well as lower toxicity when compared to the free drug.[12]

Encapsulation of pharmaceuticals through physical interaction with dendrimers leaves the pharmaceuticals unchanged. The disadvantage is that only low loadings of the pharmaceuticals are possible. Another disadvantage is that there is no control

over the release kinetics of the pharmaceutical. An alternative approach to encapsulation is to chemically bind the pharmaceutical to the dendrimer molecule. This is usually done by direct reaction with functional groups on the dendrimer or through a linker molecule if the required functional groups are not present. This can also be done by incorporation of the pharmaceutical into the dendritic architecture. The conjugation of pharmaceuticals to dendrimers through chemical bonding is called the pro-drug approach.

1.2.4.1.2 Use as synthetic proteins

Due to the very narrow size distribution of dendrimers, when compared to for instance with linear polymers, research has gone into using dendrimers as artificial proteins. A good example is the PAMAM family of dendrimers. The ammonia cored PAMAM generations 3, 4 and 5 dendrimers are very near in size and shape to the proteins insulin, cytochrome and haemoglobin respectively.[10] However, one must keep in mind that there are very significant differences between these proteins and their analogous dendrimers. Singh reported the use of dendrimers as scaffolds linking them to proteins as well as antibodies.[13] Singh synthesized a new protein-dendrimer conjugate that coupled two proteins namely calf intestine alkaline phosphatase and a fragment of an antibody to create a multifunctional protein-dendrimer conjugate.[13]

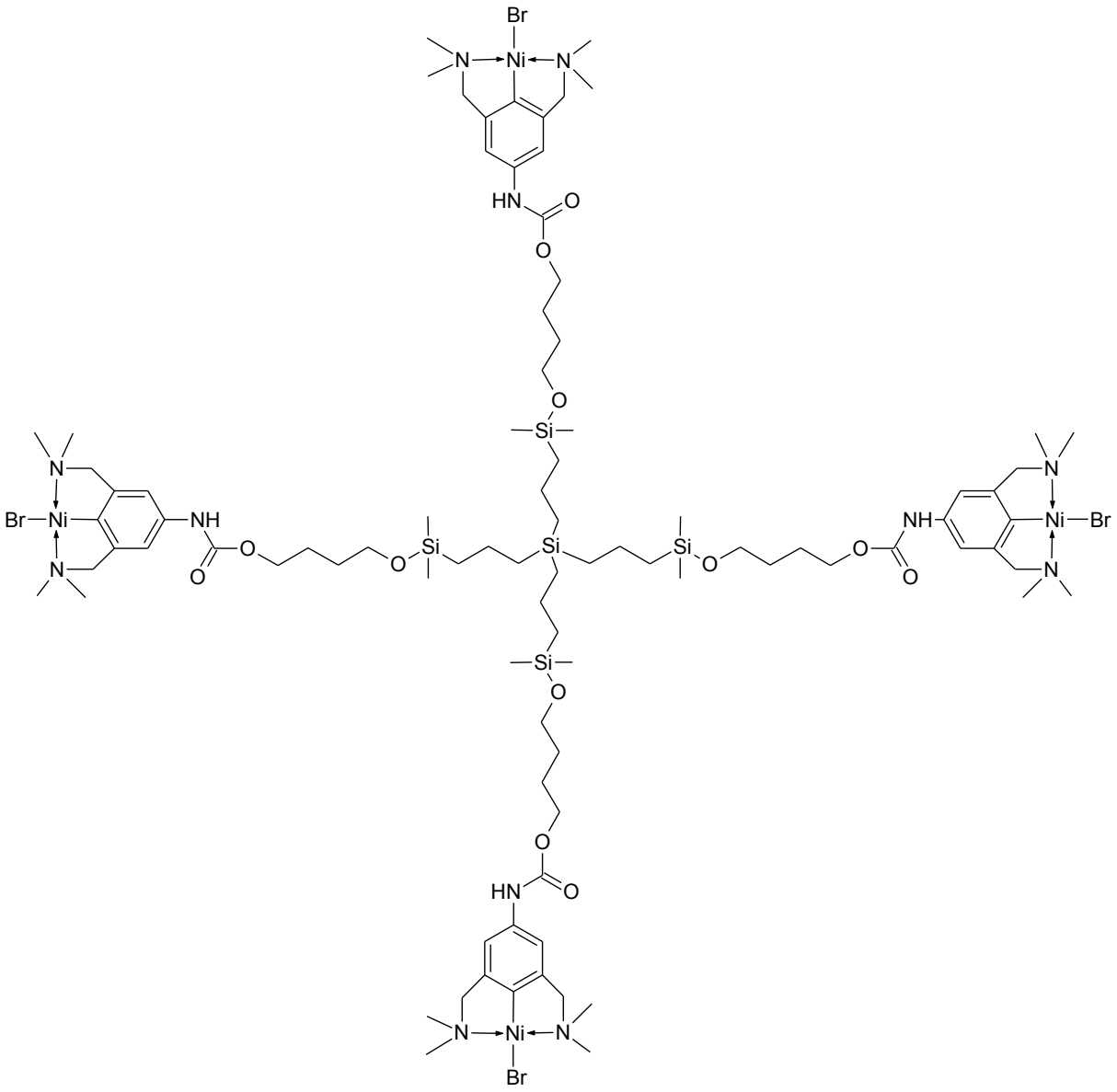
1.2.4.2 Use of dendrimers in catalysis

Catalyst recovery remains a major drawback of homogeneous catalysis. In an attempt to circumvent this problem, transition metal complexes of dendrimers called metallodendrimers are increasingly employed in catalytic applications. The use of metallodendrimers is advantageous because both catalyst recovery and catalyst removal from the product stream can be realized by using metallodendrimers.[14,15] Dendrimers can often be removed via ultra filtration and recovered. Dendrimers have also been successfully employed in continuous flow membrane reactors.[16]

The first reported use of a metallodendrimer for catalysis appeared in 1994 by the group of van Koten.[16]

Organometallic polysilane dendrimers as shown in Figure 1.3 were synthesized and tested as catalysts in the Kharasch addition reaction.[17] The dendrimer systems

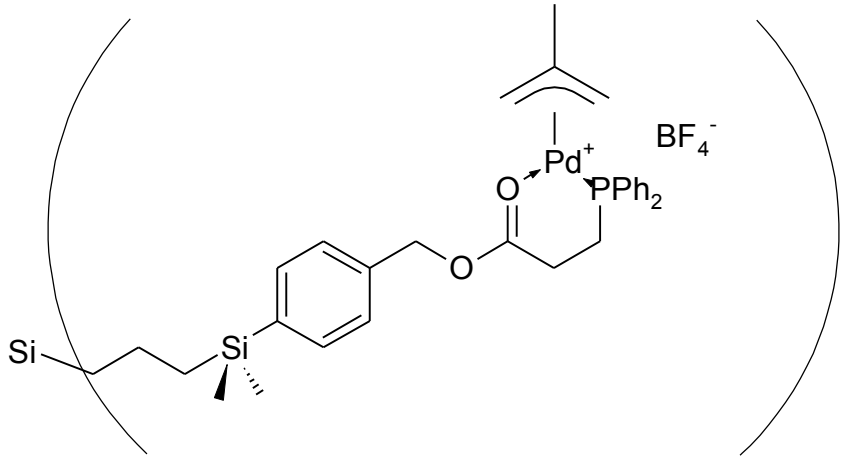
showed a drop in activity of around 20% for the first generation dendrimer and 30% for the second generation dendrimer when compared to the monomeric metal complex.



A

Figure 1.3: First generation metallodendrimer synthesized by van Koten *et al* [17]

Van Koten *et al.* later reported the synthesis of a new carbosilane dendrimer with various diphenylphosphanylcarboxylic ester end groups.[16] The P,O ligand system was utilized to synthesize the corresponding palladium metallodendrimer shown in Figure 1.4.



B

Figure 1.4: Carbosilane metallodendrimer synthesized by van Koten [16]

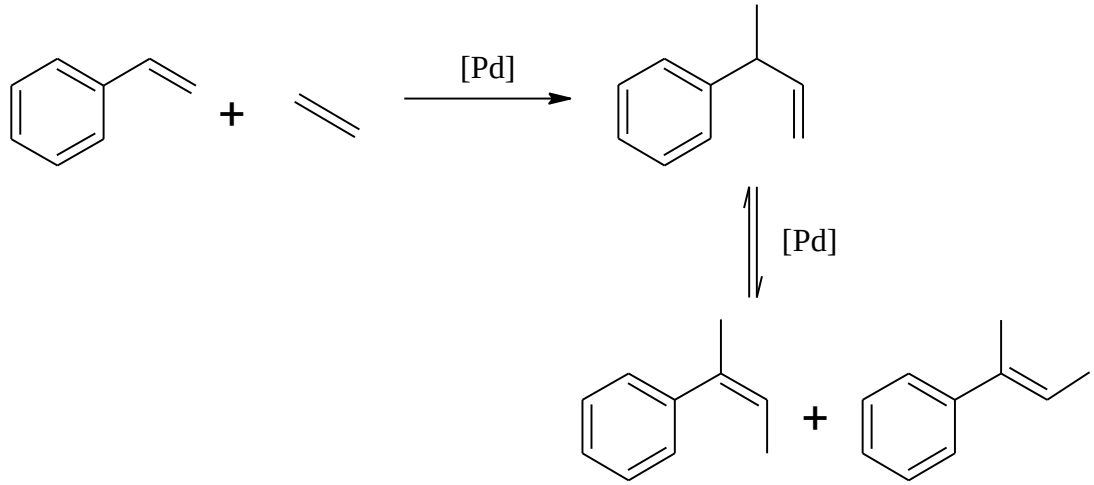
The above metallodendrimer was then utilized in the hydrovinylation of styrene. The synthesized metallodendrimers were compared to appropriate model systems. It was concluded that the model systems were more active than their dendritic counterparts and that the more active catalysts have a 7 membered Pd-P,O ring system rather than a 6 membered ring system. However, the dendritic catalysts could be run in a continuous high-pressure membrane reactor to easily separate the catalyst from the product stream. The catalysis results obtained are summarized in Table 1.1.

It was observed that the model complexes (Table 1.1 entries 2 and 5) are more active than the corresponding dendritic catalyst. A comparison between the dendritic catalyst and the model catalyst shows that after 3 hours (entries 4 and 5) the model complex has converted nearly all of the styrene while the dendritic catalyst shows very low conversion. However, initially the product 3-phenylbut-1-ene is formed but this isomerizes to an E/Z mixture of 2-phenylbut-2-ene at high conversion as shown in Scheme 1.2. It is therefore beneficial to run the catalytic reaction for a longer reaction time but at low conversion. The catalytic reaction was then run for the first time in a continuous high pressure membrane reactor (as opposed to the batch reactors used in entries 1-5) utilizing the G_0 metallodendrimer as catalyst (entry 6). It was observed that under these conditions almost no isomerization of 3-phenylbut-1-ene took place leading to an increase in the selectivity of the reaction.

Table 1.1: Catalytic hydrovinylation of styrene with metallodendrimers[16]

Entry	Ligand	Conv (%)	yield (%)
1	G_0-$(CH_2)_2$-PPh_2	68.1	56.8
2	$C_6H_5CH_2OCO(CH_2)_2PPh_2$	96.9	49.5
3	G_0-$(CH_2)_3$-PPh_2	99.9	0.2
4	G_0-$(CH_2)_3$-PPh_2[b]	3.4	3.2
5	$C_6H_5CH_2OCO(CH_2)_3PPh_2$	99.9	4.4
6	G_0-$(CH_2)_3$-PPh_2[a]	8.1	7.6

Reaction conditions: DCM (20 ml), 17 hours, 25 °C, styrene/Pd = 500 -1000, styrene (34.8 mmol) and 30 bar ethylene pressure. [a] Continuous run for 9 hours in a membrane reactor at 23°C at 30 bar ethylene pressure.[b] Reaction stopped after 3 hours. Entries 2 and 5 are model complexes.

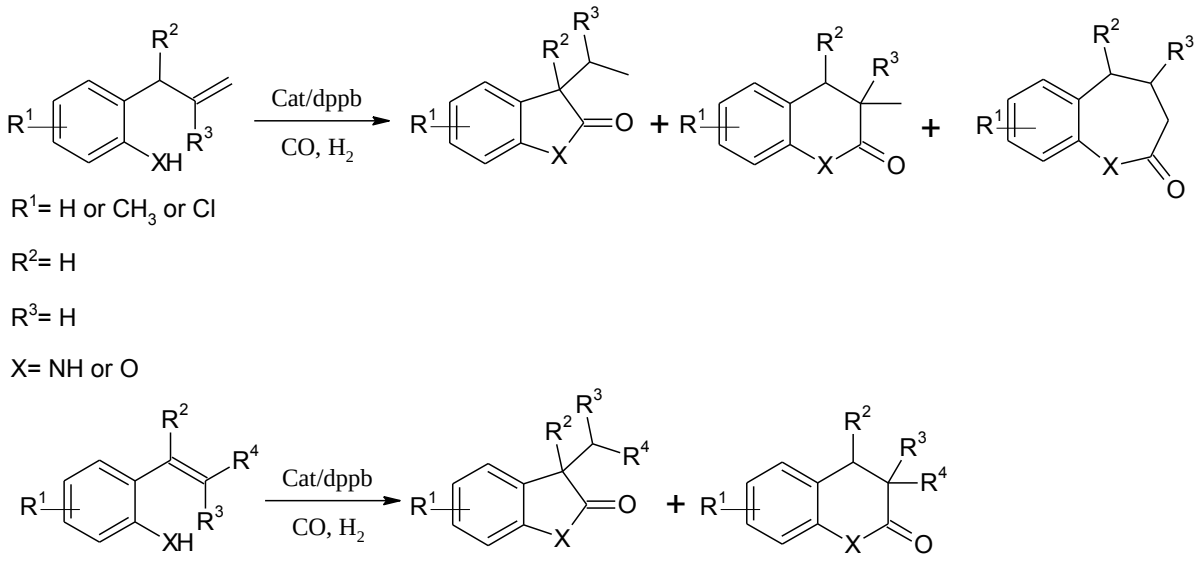


Scheme 1.2: Hydrovinylation of styrene and isomerization of products by dendritic catalysts

The reaction was run continuously in a pressure membrane reactor equipped with a filtration membrane to separate the metallodendrimer catalyst from the product. They found that catalyst retention for the G_0 dendrimer to be 85% after 9 hours. Van Koten and co-workers reported the catalytic transformation using the generation 1 dendrimer that has a total of 12 coordinated palladium ions. They found that the activity of the generation 0 and generation 1 dendrimers are fairly similar and

attributed this to the formation of palladium black and then subsequent catalyst washout. Higher generation dendrimers however, allow for much higher retention of the catalyst and represents a very successful attempt at immobilization of the catalyst.

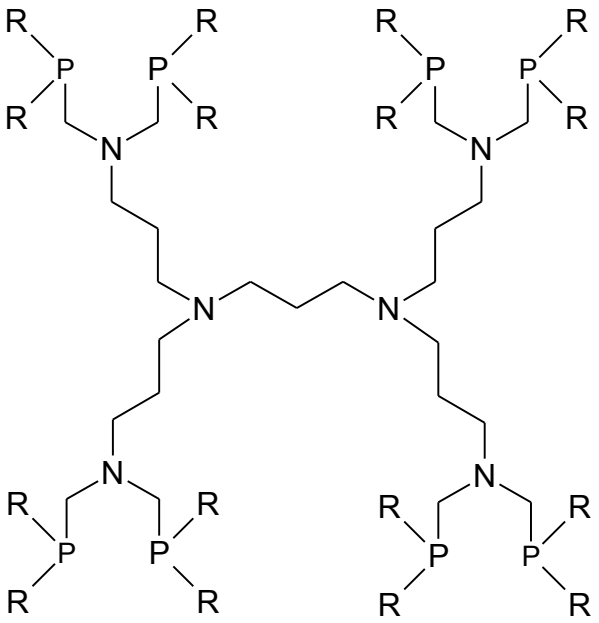
Alper and co-workers reported the synthesis of a rhodium hydroformylation catalyst anchored to PAMAM-dendronized silica gel supports.[18] The researchers also introduced dendronized polystyrene resins as support for rhodium catalysts in hydroformylation reactions of aryl olefins and vinyl esters.[15] The catalytic system gave very good conversion. The dendritic system also gave excellent selectivity towards the formation of the branched aldehyde. The same researchers also reported the synthesis of palladium metallodendrimers supported on silica followed by the synthesis of the corresponding palladium metallodendrimer. Metallodendrimer generations 0-3 were successfully used as catalysts for the cyclocarbonylation of 2-allylphenol, 2-allylaniline, 2-vinylphenol and 2-vinylaniline to afford the corresponding five, six or seven membered lactones and lactams as shown in Scheme1.3.



Scheme 1.3: Catalytic carbonylation with metallodendrimers to form lactones and lactams [13]

Good conversions were obtained for the silica supported dendronized catalysts and in some cases superior regioselectivity was observed when comparing the dendronized catalyst to the corresponding homogeneous system. The dendronized catalyst could be recycled and reused 3-5 times. Further work done by the group of Alper. includes the use of metallodendrimers as catalysts for oxidation,[19] hydrogenation[20], and C-C coupling reactions.[21]

Méry and Astruc reported the synthesis of a dendritic cis-bis-phosphine ligand.[22] Reaction with Hoveyda's catalyst yielded the cis-bis-phosphine benzylidene ruthenium complexes. The metallodendrimers obtained and appropriate model complexes were tested as catalysts for the ring opening metathesis polymerization (ROMP) of norbornene.



R= t-butyl

C

Figure 1.5: Dendrimer synthesized by Méry and Astruc [22]

They found a positive dendritic effect whereby the dendritic catalysts achieved 99 % conversion much quicker than the model homogeneous catalyst. It was hypothesized that dissociation of a phosphine ligand was easier in the dendritic system thereby initiation of ROMP occurs much more rapidly for the dendritic system. These systems also showed a negative dendritic effect whereby reaction times for the same conversion increased as the dendrimer generation increased.[22]

Dendrimer encapsulated nanoparticles (DENs) have also been used as catalysts for a variety of processes. In 1998 the research group of Crooks and co-workers reported the synthesis of these dendrimer encapsulated metal nanoparticles.[23] They used amine terminated PAMAM dendrimers as well as alcohol terminated PAMAM dendrimers to coordinate Cu^{2+} ions to the dendrimer followed by reduction using $NaBH_4$. This resulted in the formation of intradendrimer Cu clusters. They found that the dendrimer acts as a template molecule and helps control the size of the nanoparticles produced and can lead to fairly monodisperse nanoparticles. These

systems have been applied in various catalytic applications. Crooks *et al.* used dendrimer encapsulated Pt and Pd nanoparticles in the catalytic hydrogenation of alkenes.[24] Table 1.2 shows the results of the catalytic experiments performed with these dendrimer encapsulated nanoparticles. They found that the higher generation dendrimers (entry 3) acts as a filter to the nanoparticles. The higher generation dendrimers are less porous and do not allow easy access to the nanoparticles influencing the reaction rate and leading to a negative dendrimer-effect being observed in terms of the reaction rate.

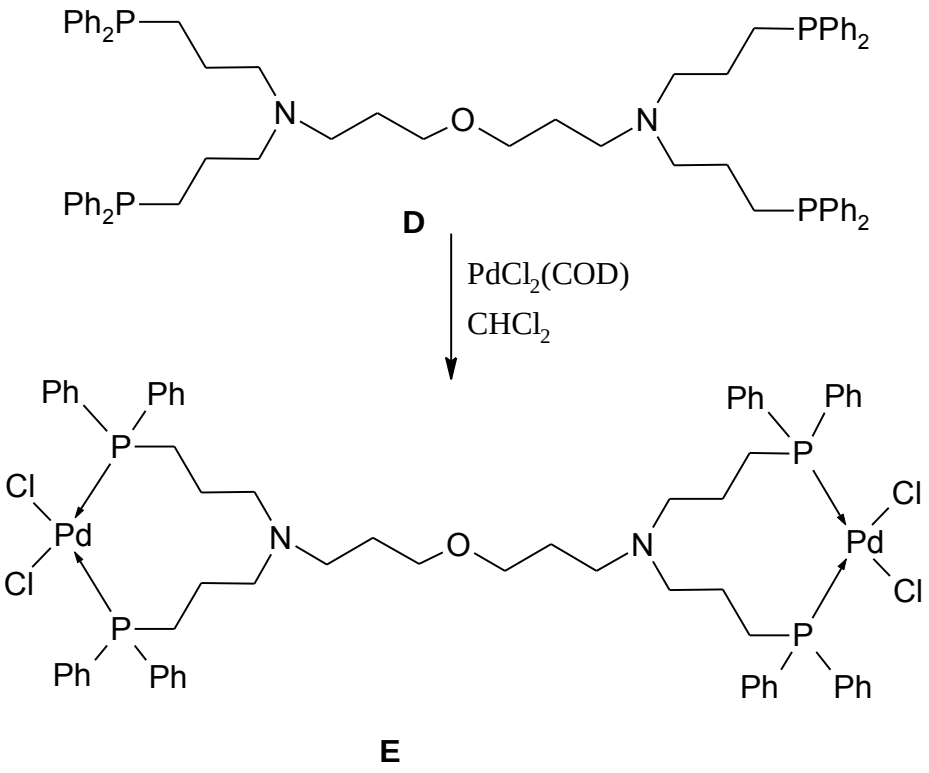
Furthermore, a catalytic experiment was performed with both the branched and linear alkenes. The dendrimer generations 6 and 8 dendrimers would only allow the linear alkene through the sterically crowded dendrimer to afford access to the metal nanoparticles. Thus selective catalysis is possible using these dendritic systems.

Table 1.2: Catalytic hydrogenation of alkenes using DENS[24]

Entry	Catalyst	TOF	
		N-Isopropyl acrylamide	allyl Alcohol
1	G4-OH(Pd)	372	218
2	G6-OH(Pd)	42	201
3	G8-OH(Pd)	17	134
4	G4-OH(Pt)	57	25
5	G6-OH(Pt)	30	

The dendrimer also acts as stabilizer and prevents aggregation of the nanoparticles. Dendrimer stabilized metal nanoparticles often exhibit better selectivity in catalytic reactions compared to the unsupported systems. It is believed that the dendrimer controls access of the substrate to the metal nanoparticles leading to the enhanced selectivity.

Krishna and Jayaraman reported the synthesis of poly(etherimine) dendrimers in 2004.[25] They then proceeded to synthesize the corresponding Pd(II) metallodendrimer as depicted in Scheme 1.4.



Scheme 1.4: Synthesis of a polyetherimine metallodendrimer[25]

These new metallodendrimers were then tested as catalysts in the Heck reaction utilizing a range of different olefin substrates with iodobenzene. The researchers found that the dendritic catalysts yielded high conversion, performing better than the monomeric analogue. A general trend was observed for the dendritic catalysts where the higher generation metallodendrimer catalysts performed better than low generation dendrimers. The generation 3 metallodendrimer displayed a higher turnover number (TON) than the generation 2 and 1 metallodendrimers thus indicating a positive dendrimer effect for these catalysts.

The above mentioned studies demonstrate the potential advantages of using dendrimer catalysts which can potentially be recycled, show enhanced activity and better selectivity.

1.3 Macrocycles

The International Union of Pure and Applied Chemistry (IUPAC) define a macrocycle as: “A cyclic macromolecule or a macromolecular cyclic portion of a macromolecule.”.[26] Macrocycles are also often defined as macromolecules with at least 3 donor atoms capable of coordinating to a metal ion and with a ring size of at least 9 atoms.

1.3.1 History of macrocycles

The first report of the synthesis of cyclic poly-sulfonamides was published in the year 1954 by Stetter and Roos.[27] They reported that the reaction of terminal halides with bis-sulfonamide sodium salts, under conditions of high dilution, yielded the macrocyclic sulfonamides in moderate yields.

The first systematic study of crown ethers and their complexes of alkali and alkali earth metals was done by Pedersen in 1967.[28] Pedersen had attempted the synthesis of bis[2-(o-hydroxyphenoxy)ethyl] ether by reacting bis(2-chloroethyl)ether with the sodium salt of 2-(o-hydroxyphen-oxy)tetrahydropyran. A small impurity of catechol led to the formation of white crystals as a side product. Subsequent analysis of the white crystals showed that the material formed was, a cyclic polyether. Cyclic polyethers were previously reported by others. Luttringhaus and Ziegler reported cyclic polyethers synthesized from catechol.[29] Adams and Whitehill synthesized cyclic polyethers from hydroquinone.[30] Ackman, Brown and Wright synthesized the cyclic polyether, 2,2,7,7,12,12,17,17-octamethyl-21,22,-23,24 tetraoxaquaterene by the condensation of acetone with furan.[31] Down *et al.* synthesized the cyclic tetramer of propylene oxide.[32] They found that the cyclic propylene oxide was able to solvate a small amount of an eutectic mixture of sodium and potassium to give blue solutions of solvated electrons and cations.

Of these authors Pederson was the first to synthesize stable complexes of the cyclic polyethers with alkali or alkali earth metals. Pederson synthesized a library of 33 cyclic polyethers which were capable of forming stable 1:1 complexes with the alkali and alkali earth metals.[29] Prior to Pederson’s paper in 1967, a use for these cyclic

polyether molecules was yet to be found. The discovery of the crown ether's remarkable coordinating ability led to intense research into the field of crown ether macrocycles.

1.3.2 Synthesis of macrocycles

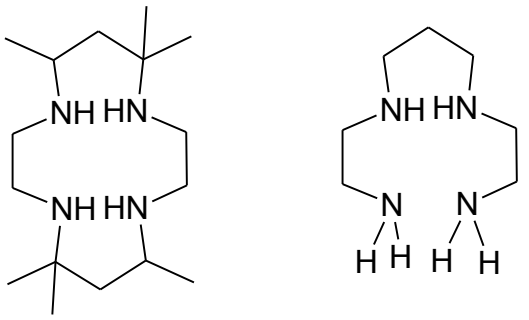
There are two synthetic methodologies commonly employed in the synthesis of macrocyclic compounds. These are high dilution synthesis or template synthesis.[33] Working with large volumes of solvent (high dilution) limits the extent to which reactants will oligomerize or polymerize. Another approach is to coordinate the open chain reactant to a suitable metal ion bringing the mutually reactive end groups into close proximity to close the ring in an attempt to avoid reactants polymerizing or oligomerizing.

1.3.3 Properties of macrocycles

Macrocycles have received considerable research interest due to their unique properties namely the macrocyclic effect and macrocyclic pre-organisation.

1.3.3.1 The macrocyclic effect

Chelation is the formation of two or more coordinate bonds in the same ligand to a single metal ion. Chelating ligands exhibit a *chelate effect* whereby the polydentate ligand forms a thermodynamically more stable complex than the monodentate analogues. The stability of macrocyclic complexes are additionally enhanced by a macrocyclic effect first reported by Cabbiness and Margerum.[34] These researchers determined stability constants for the ligands **G** and **H** (shown in Figure 1.6) with copper ions comparing the stability of the macrocyclic copper complex with that of its open chain analogue.



G **H**

Figure 1.6: Macrocycle vs open chain analogue

It was found that the macrocyclic complex was 10 000 times more stable than its open chain analogue. They observed that such a large increase in stability cannot be attributed to the chelate effect alone. The observed macrocyclic effect increased stability 10 times more than the chelate effect for their copper amine complex systems. The authors hypothesized that the configuration (pre configuration) and solvation of the free macrocyclic ligand was responsible for the large increase in stability over the open chain analogue.

1.3.3.2 Macrocyclic pre-organisation

The term “pre-organisation” was first coined by Cram *et al*.[35] A pre-organised ligand, a free ligand that is structurally similar to the final structure it will adopt upon complex formation, has both entropic and enthalpic advantages over its open chain counterpart. Upon complex formation a pre-organised ligand’s strain energy does not increase remarkably since the structural configuration does not change much. Furthermore a pre-organised ligand’s donor atoms are usually in close proximity. This leads to electrostatic repulsions in the free ligand. Upon complex formation this repulsion is released. These two factors both contribute to give an overall enthalpy advantage over the normal (unorganised) ligand. A pre –organised ligand has limited space available for solvent molecules. Removing the solvent molecules may therefore require much less energy compared to their unorganised ligand. As a general rule macrocyclic ligands are more pre-organised than their open chain analogues.[36]

1.3.4 Applications of macrocycles

The applications of macrocycles have shown considerable growth since the discovery of stable macrocyclic complexes. Macrocycles are often used as ligands in metal extraction.[37] Macrocycle complexes also find use in various medical applications [38] and in the field of catalysis.[39]

1.3.4.1 Metal extraction

A high demand for processes to recover heavy and precious metals from waste streams exist. Heavy metals are often found in waste streams stemming from their industrial use. These metals can pose a serious human health risk due to their toxicity, especially the metals chromium, cadmium, lead and mercury. Extraction of the precious metals such as silver, gold, platinum and palladium is also of interest due to their commercial value. Processes to remove these metals from waste streams are therefore of particular interest. Macrocyclic ligands have successfully been used to recover both heavy and precious metals.

Shinkai *et al.* reported the extraction of heavy metals especially Pb(II), through the use of an azobenzene-bridged crown ether. [40] This compound exhibits photoinduced cis-trans isomerization. They found that the trans isomer extracted considerable amounts of the metal ions, Cu^{2+}, Ni^{2+}, Co^{2+}, Pb^{2+} and Hg^{2+} while the *cis* isomer showed much less extraction ability. It was concluded that in the *trans* configuration the azopyridine-bridge nitrogens are able to coordinate to a metal ion, forming a stable complex, while in the *cis* configuration this is not possible.

The extraction of metals with azamacrocycles was investigated by Zhao and Ford.[41] They synthesized N-substituted derivatives of the macrocycle [18]-N_6 as shown in Figure 1.7. Synthesized macrocycles were tested in metal ion extraction and transport studies. The researchers found that transition and heavy metal picrates were effectively extracted from water to chloroform but alkali and alkali earth metal picrates were not extracted. Extraction studies indicated that compound **I3** showed selectivity towards the extraction of Cu^{2+}, Ag^{+} and Pb^{2+}. The hexamide **I2** effectively extracted Cu^{2+}, Ag^{+}, and Hg^{2+} but only transports Cu^{2+} and Ag^{+}.

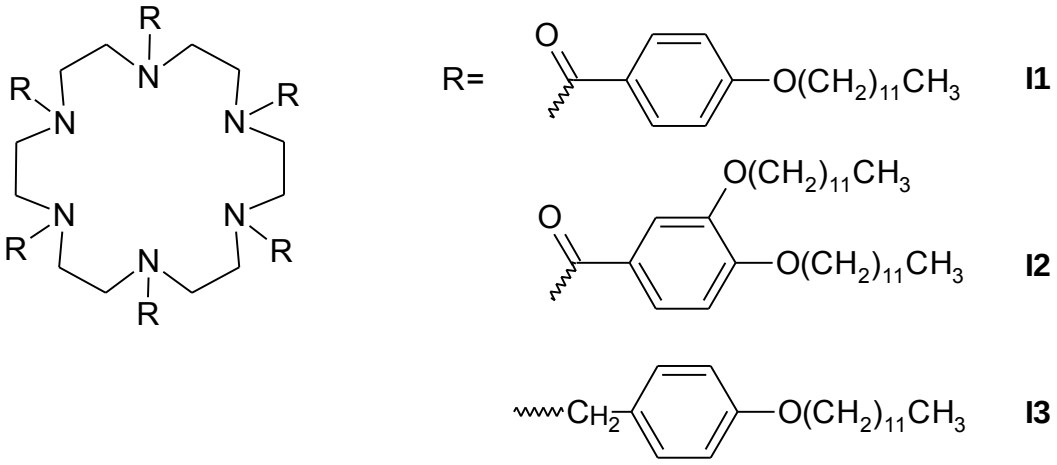


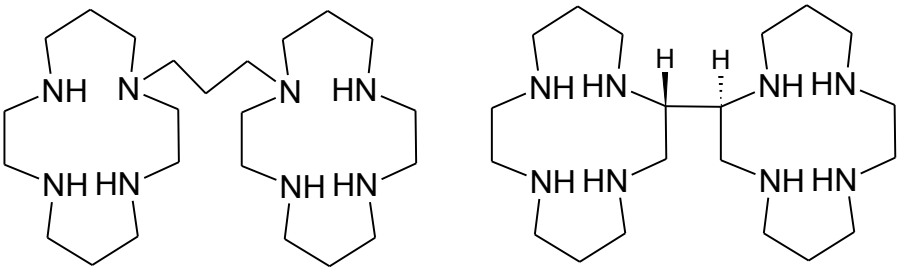
Figure 1.7: Macrocycles synthesized by Zhao and Ford [41]

1.3.4.2 Medical applications

Macrocycles, especially, cyclam (1,4,8,11-tetraazacyclotetradecane), have received widespread interest from medicinal chemists due to the potential these compounds show for the treatment of acquired immunodeficiency syndrome (AIDS).[38] Furthermore macrocyclic complexes are often used in radiopharmaceuticals for the treatment of cancer.[42]

1.3.4.2.1 Treatment of HIV / AIDS using macrocyclic complexes

Unmetallated macrocyclic compounds such as cyclam have been shown to possess anti HIV activity. In a study done by de Clercq and co-workers, cyclam was tested against HIV-1 and HIV-2 strains of the virus.[43] They found that cyclam had a slight inhibitory activity against HIV-1 and HIV-2 strains of the virus. The researchers also synthesized bicyclam compounds (Shown in Figure 1.8) and tested them against HIV-1 and HIV-2 strains. These linked bicyclams showed high inhibitory activity towards both HIV-1 and HIV-2. The bicyclam compound **J** (named **JM2763** by the author) linked with a propyl chain as well as the bicyclam **K** (**JM1657**) linked through the carbon skeleton showed remarkably high inhibitory activity against HIV-1 and HIV-2 strains.



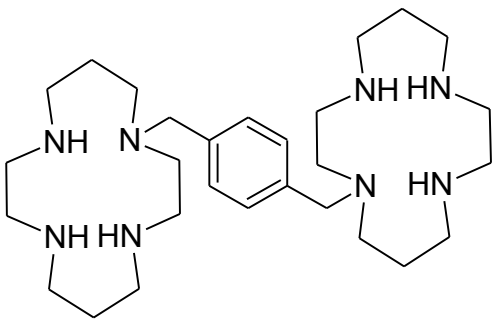
JM2763 JM1657

J **K**

Figure 1.8: Bicyclams JM2763 and JM1657 tested against HIV[43]

The authors found that these compounds inhibit an early event in the virus replication process most likely the viral uncoating event.[43]

De Clercq *et al.* also synthesized the bicyclam **L** (Figure 1.9) with an aromatic linker.[44] This compound is one of the most inhibitory compounds yet synthesized. Complexes of bicyclam are also known to inhibit HIV. The zinc complex of **L** is slightly more active against HIV than the free **L**. Complexes of **L** target the initial events in the replicative cycle namely the virus adsorption to the cell and the virus cell fusion steps.



JM3100

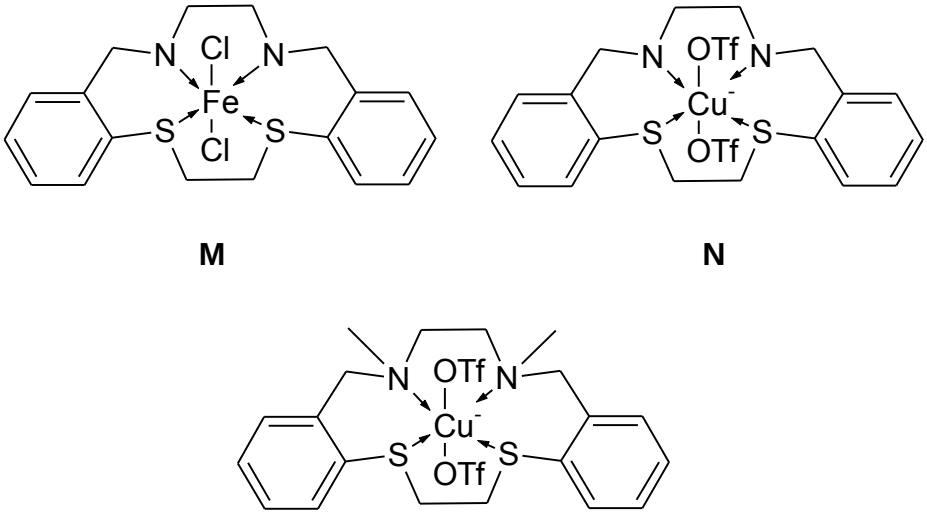
L

Figure 1.9: Bicyclam JM3100 used as HIV inhibitor[44]

1.3.4.3 Use of macrocycles in catalysis

Transition metal complexes of macrocycles have been successfully employed in catalytic applications. The Mn complex of TACN (1,4,7-Triazacyclononane) is known to be a very active catalyst for the epoxidation of olefins.[45-,47] The Cu(II) macrocyclic complexes of TACN, cyclam and cyclen (1,4,7,10-tetraazacyclododecane) encapsulated in zeolites were shown to be active catalysts in the oxidation of ethyl benzene.[48] Transition metal complexes of mixed donor N2-S2 macrocycles are active alkane oxidation catalysts.[49]

Pombeiro *et al.* reported the synthesis and characterization of new Fe(II) and Cu(II) mixed donor macrocycle complexes.[49] These novel complexes were tested as catalyst precursors for the oxidation of cyclohexane to cyclohexanol. The complexes **M**-**O** were all catalytically active in the presence of H_2O_2.



M **N**

O

Figure 1.10: Complexes synthesized by Pombeiro et al [49]

The results obtained for the catalytic experiments performed with these complexes are summarized in Table 1.3 which shows the total yield of cyclohexanol and cyclohexanone formed. The Fe(II) complex **M** was found to be most active in the

catalytic oxidation of cyclohexane, showing relatively high conversion. The best results were obtained using trifluoromethansulfonic acid (TfOH) as additive (Table 1.3 entry 4). The complex is selective for the formation of cyclohexanol (CyOH) over the formation of cyclohexanone (CyO). The Cu(II) complexes **N** and **O** were less active than the Fe(II) complex but were also selective towards cyclohexanol formation. Complexes **M-O** also exhibited high catalytic activity in the microwave assisted solvent free oxidation of 1-phenylethanol by tert-butyl-hydroperoxide. However, the Cu(II) complexes **N** and **O** were slightly better than complex **M** with complex **N** achieving the highest conversion.

Table 1.3: Catalytic oxidation of cyclohexane to cyclohexanol and cyclohexanone[49]

Entry	Additive	Yield %					
		M		**N**		**O**	
		CyOH	CyO	CyOH	CyO	CyOH	CyO
1	None	1.7	0.8	6.5	1.8	8.3	2
2	Hpca	15.2	2.3	0.2	0.2	0.1	0.1
3	HNO_3	15.2	4	4.2	1.6	5.4	1.9
4	TfOH	19.2	2.1	4.4	1.7	4.3	1.7
5	TFA	16.9	3.1	4.5	1.5	4.6	1.5

Reaction Conditions: acetonitrile (3 ml), cyclohexane (5 mmol), catalyst (0.2 mol%, 5 mmol), H_2O_2 (7 mmol), acid additive, 6 hours at 25 °C

1.4 Macrocycle-dendrimer-conjugates

Dendritic compounds containing macrocycles in their architecture have been described in recent literature though reports of such compounds remain rather rare.[50] These compounds often exhibited interesting effects arising from both the dendrimer and macrocycle parts.[50]

1.4.1 Different types of macrocycle-dendrimer conjugates

These conjugates can be categorized according to the position of the macrocycle. The red ellipse in Figure 1.11 represents a macrocycle. Figure 1.11 shows the different types of dendrimer-macrocycle conjugates that have been synthesized. Dendrimers have been synthesized with a macrocycle (red ellipse) at its core (**MD1**). Other dendrimers are functionalized at the periphery with macrocycles (**MD2**). Dendrimers are known with both macrocycle peripheries and a macrocyclic core (**MD3**). Dendrimers have also been synthesized where macrocycles are attached to the internal layer (**MD4**). Molecules with a macrocycle in each dendrimer layer are also known (**MD5**). Dendrimers of the type **MD6** have been synthesized these dendrimers possess a macrocycle in the internal branches of the dendrimer.

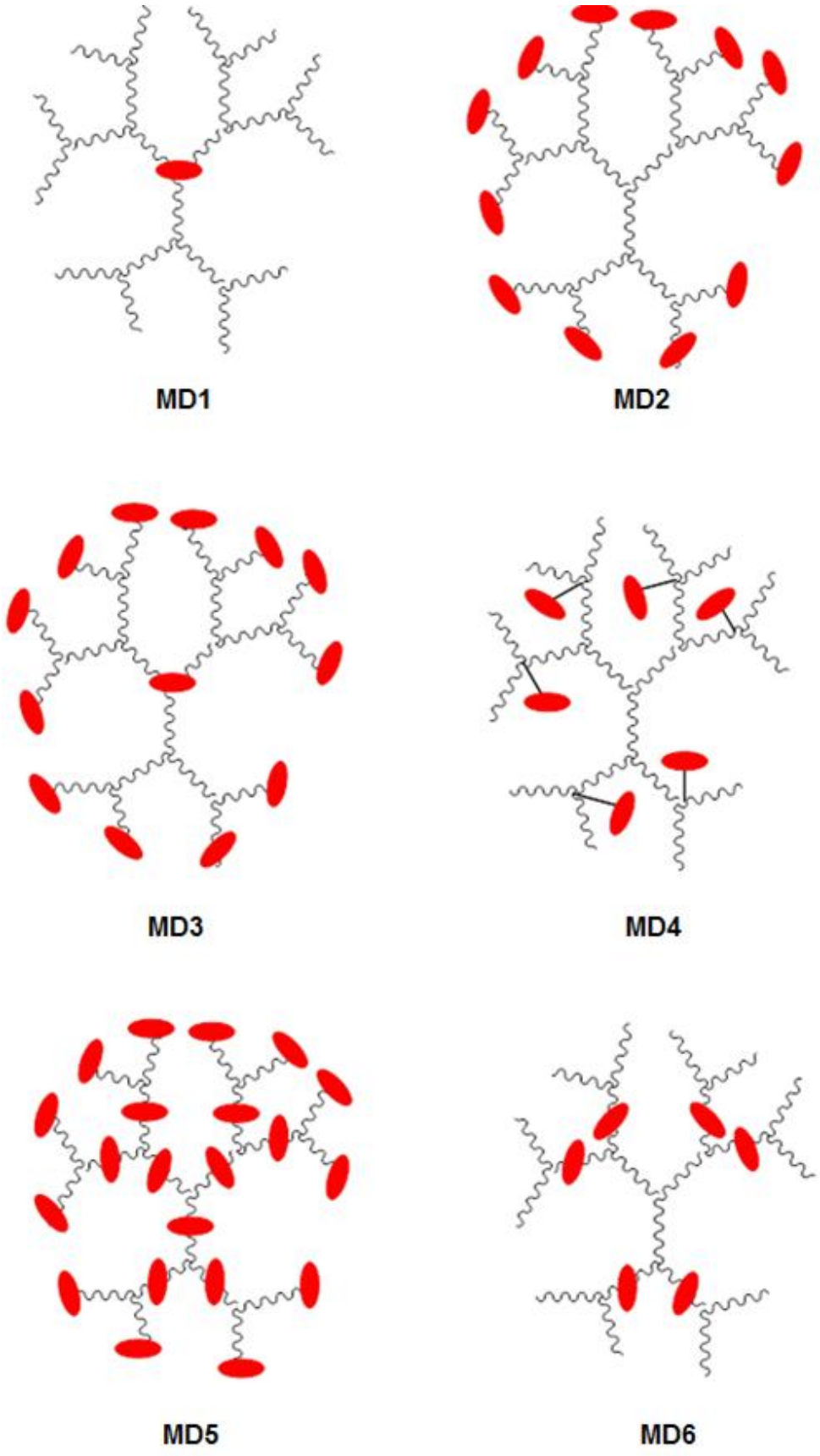
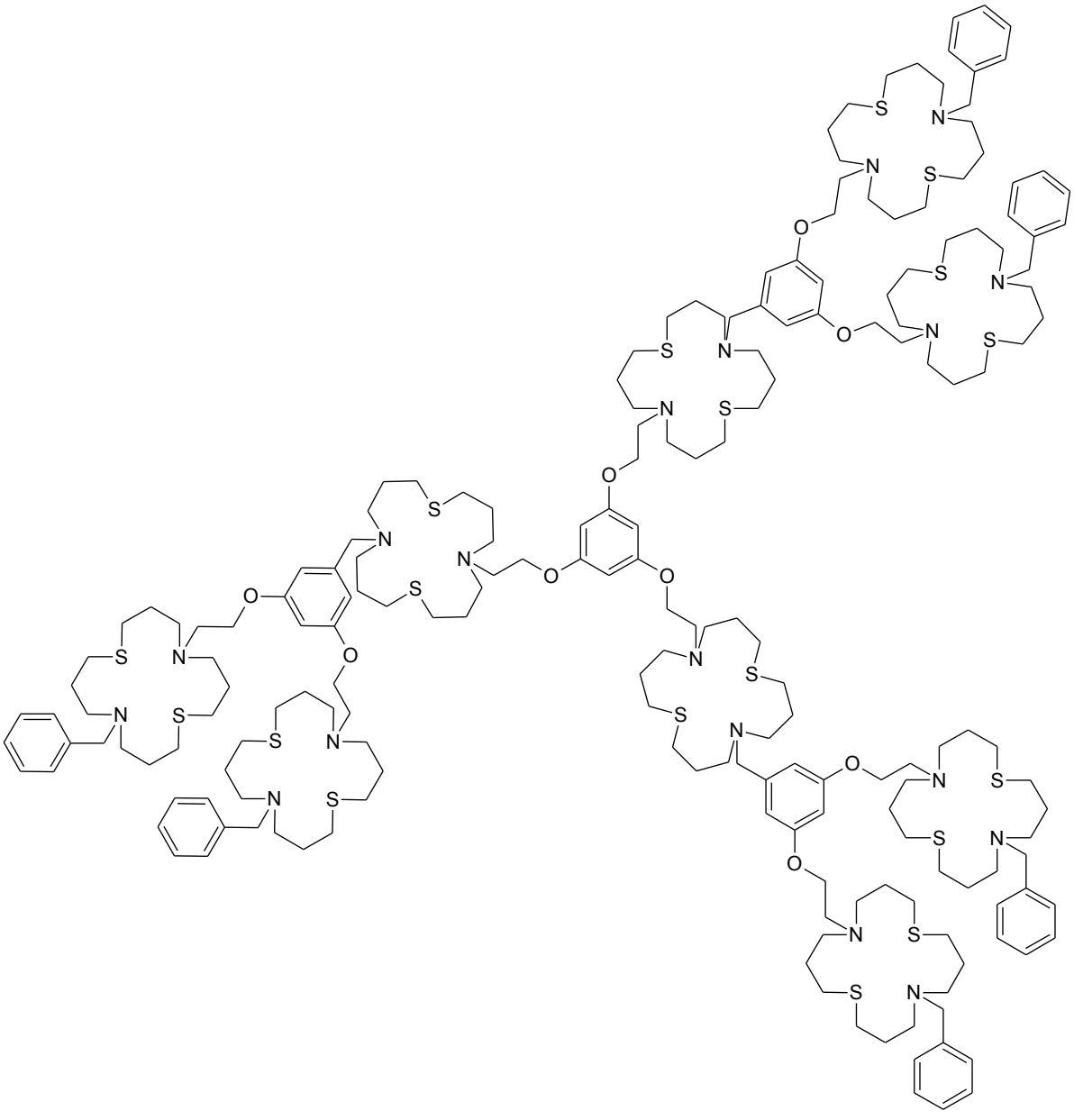


Figure 1.11: The 6 types of macrocycle-dendrimer conjugates

1.4.2 Examples of macrocycle-dendrimer conjugates

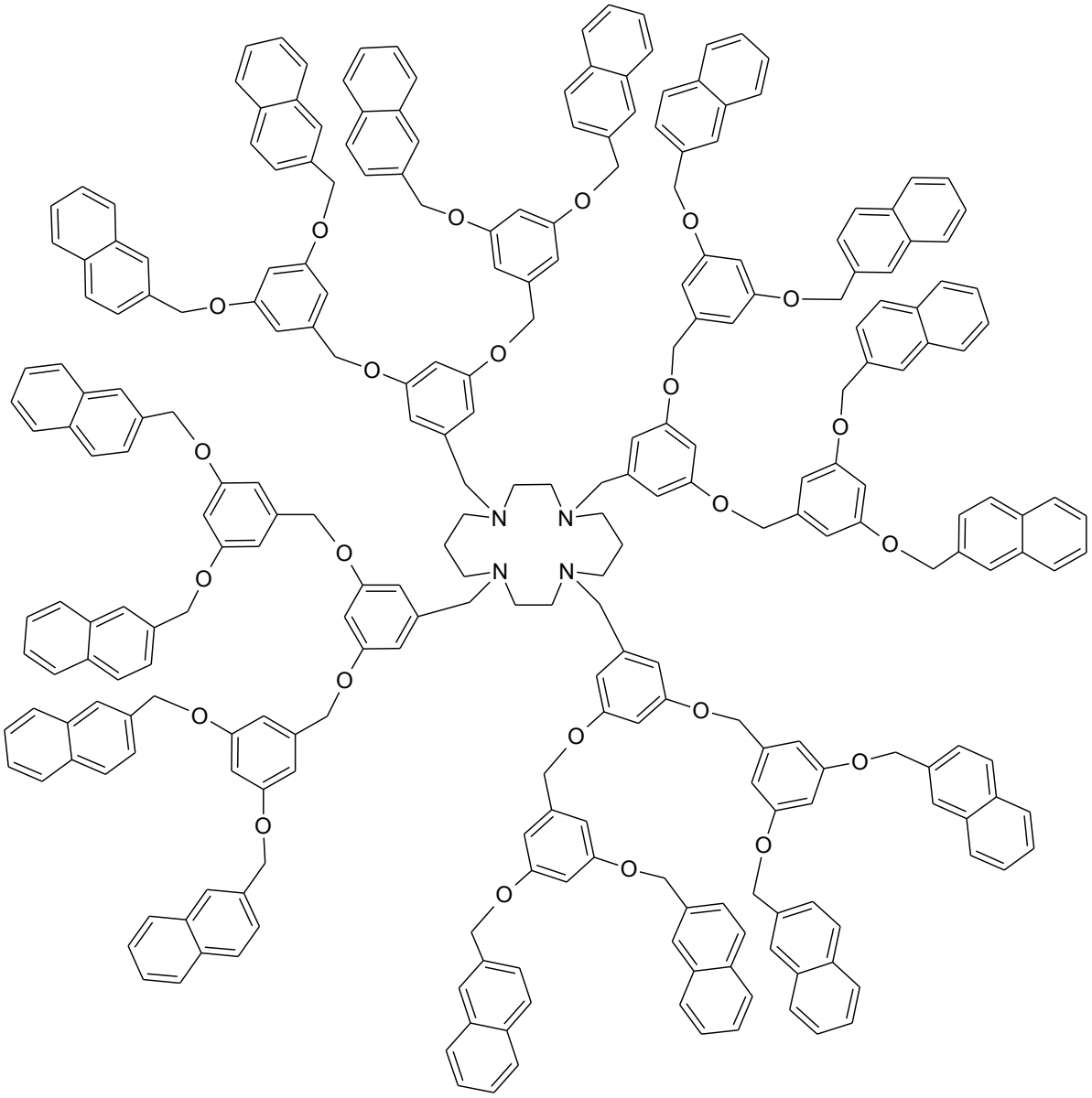
Lindoy and co-workers reported the synthesis of a second generation macrocycle dendrimer conjugate.[51] The dendrimer **P** (shown in Figure 1.12) incorporates a total of 9 S2 N2 mixed donor macrocycles into its architecture. Furthermore a palladium metallo-dendrimer was successfully synthesized using this conjugate and yielding a molecule with 9 Pd metal centres.



P

Figure 1.12: Macrocycle-dendrimer conjugate synthesized by Lindoy[51]

Macrocycle cored dendrimers are known such as the following example, **Q** (Figure 1.13), synthesized by Vögtle.[52] The dendrimer consists of a cyclam core appended with dimethoxybenzene and naphthyl peripheries.

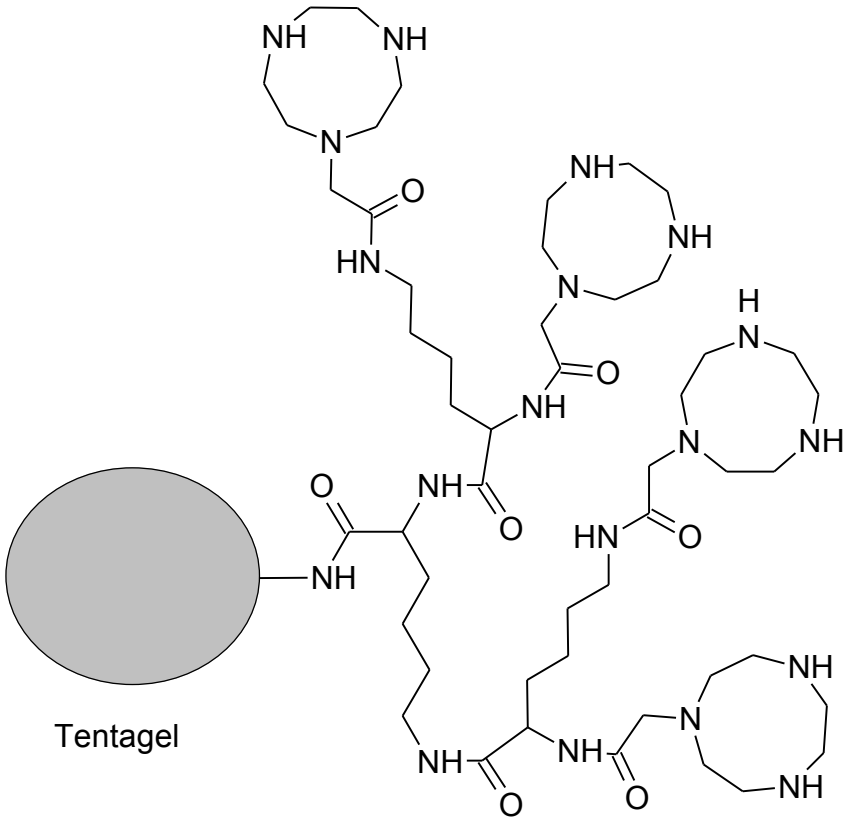


Q

Figure 1.13: Macrocycle cored dendrimer prepared by Vögtle *et al*[52]

Q was complexed with Zn^{2+} to form the metallodendrimer. However, through ^{1}H NMR titration experiments it was found that two dendrimer units coordinated one Zn^{2+} metal ion (2: 1 stoichiometry).

In 2009 Zaupa, Prins and Scrimin reported the synthesis of a dendrimer with 1,4,7-triazacyclononane (TACN) peripheries affixed to a tentagel core **R**.[53] Tentagel is a resin consisting of polystyrene-polyethyleneglycol functionalized with a lysine based dendrimer. **R** was then complexed with Zn^{2+} metal ions and then tested as catalysts for the hydrolytic cleavage of 2-hydoxypropyl-p-nitrophenyl phosphate (HPNPP) which serves as a model substrate for RNA. It was found that the higher generation dendrimer bearing 8 TACN units performed much better than the lower generation dendrimer (4 TACN units) indicating a positive dendritic effect.



R

Figure 1.14: Macrocycle on periphery of dendrimer[53]

1.5 Conclusion and aims

In summary, dendrimers are hyperbranched largely spherical macromolecules. Macrocycles are cyclic macromolecules with at least 3 donor atoms and a ring size of at least 9 atoms. Both macrocycles and dendrimers are often used in the fields of

catalysis, and medicinal chemistry. Macrocycle-dendrimer conjugates have previously been reported in the literature and often exhibit unusual properties observed in neither the parent dendrimer (monomer) nor the macrocycle.

In light of the afore-mentioned the aims of this project were:

1) The synthesis of novel macrocycle-dendrimer conjugates. This includes both dendrimers with macrocycles on the periphery as well as macrocycle cored dendrimers.

3) The synthesis of metal complexes based on some of these conjugate ligands.

2) The characterization of all synthesized ligands and complexes using a range of analytical techniques including: FT-IR and NMR spectroscopy as well as mass spectrometry.

4) Due to the previously mentioned application and advantages of both macrocycles and dendrimers in the field of catalysis, such as the potential recyclability of dendritic catalysts, synthesized metal complexes will be evaluated as catalyst precursors in the catalytic oxidation of alcohols.

1.6 Overview of thesis content by chapter

Chapter 2: The synthesis and characterization of various attempts at macrocycle-dendrimer conjugates as well as the intermediates to these materails are described in this chapter. This includes the full synthesis as well as characterization of a dendrimer with a cyclam core and salicylaldimine peripheries.

Chapter 3: Synthesis of the Cu, Ni and Zn complexes (based on ligand **16** described in Chapter 2) is discussed. Subsequently the performance of the Cu and Ni metallodendrimers are evaluated as catalyst precursors in the catalytic oxidation of benzyl alcohol to benzaldehyde.

Chapter 4: The chapter summarizes the most important aspects of the thesis according to chapter. Conclusions are drawn from the synthetic data presented in the thesis as well as the catalytic results presented in Chapter 3. Finally a few suggestions for future work are made.

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CHAPTER 2: SYNTHESIS AND CHARACTERIZATION OF DENDRITIC LIGANDS AND LIGAND PRECURSORS

2.1 Introduction

The synthesis of various macrocycle-dendrimer conjugates and intermediates are reported in this chapter. Two different types of macrocycle-dendrimer conjugates as discussed in Chapter 1.4.1 are proposed. These include dendrimers with macrocycle peripheries as well as a dendrimer with a cyclam core.

2.2 Macrocycles on the periphery of dendrimers

Dendrimers containing macrocycles at the surface (periphery) have previously been reported by others.[1, 2] Figure 2.1 demonstrates the general structure of such a system. The red ellipses represent macrocycle molecules anchored onto the surface of the dendrimer.

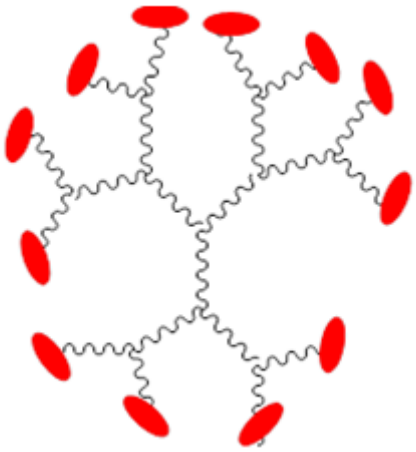


Figure 2.1: Macrocycles on the periphery of dendrimer

Synthesis of such a system was reported by Sebastian *et al*.[2] They synthesized phosphorous containing dendrimers and subsequently functionalized the dendrimer peripheries with an olefinic macrocycle. These workers initially opted to functionalize

the dendrimer core with aldehyde peripheries. The macrocycle on the other hand is functionalized with a linker molecule in order to have a pendant arm bearing a primary amine. This primary amine is then used to anchor the macrocycle to the dendrimer through a Schiff base condensation reaction with the aldehyde group to form an imine bond which is further reduced to the corresponding secondary amine using $NaBH_3CN$. Figure 2.2 shows the various components of the dendrimer under discussion.

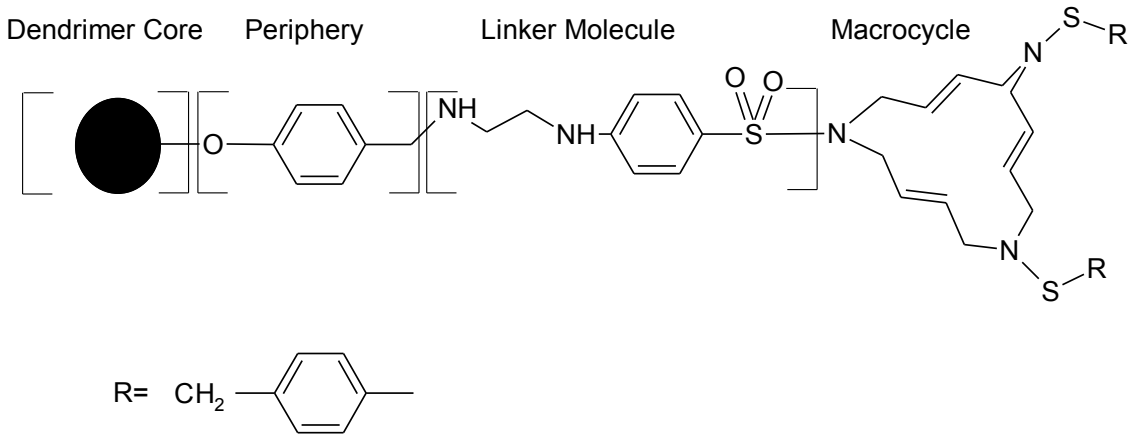
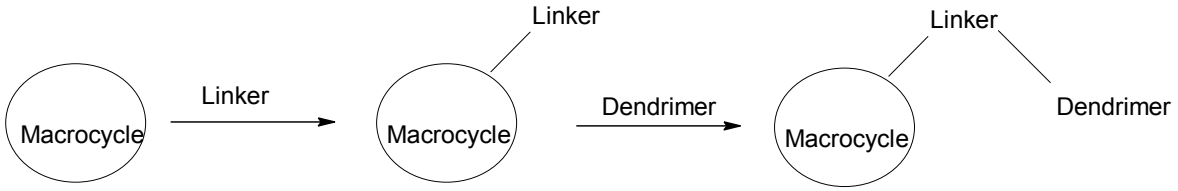


Figure 2.2: Constituents of macrocycle-dendrimer conjugates

2.2.1 Synthesis of peripherally modified polypropylenimine dendrimers with macrocyclic surface functionalities

The strategy for the surface modification of the di-aminobutane polypropylenimine (DAB PPI) dendrimers is to first functionalize a macrocycle with an appropriate linker molecule which will allow attachment to the dendrimer periphery as outlined in Scheme 2.1.

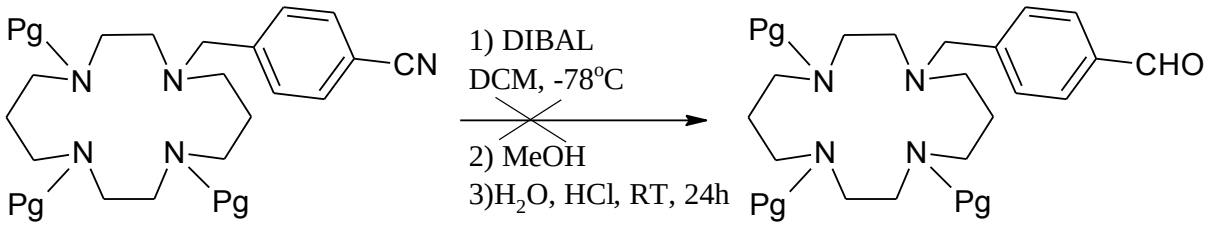


Scheme 2.1: Strategy for synthesis of DAB PPI dendrimer modified with macrocyclic units at the periphery

The linker molecule is defined as a molecule with an appropriate functional group that will allow for further reaction with the primary amine groups on the periphery of the DAB dendrimer thereby anchoring the macrocycle to the dendrimer surface. In order to prevent dimerization or crosslinking of dendrimers, the cyclam molecule should be functionalized with only one linker molecule. Several methods have been reported to accomplish this.[1]

2.2.2 Synthesis of the linker molecule

The strategy outlined above makes use of a linker molecule with appropriate functionalities for further reaction with the dendrimer periphery. An aldehyde functionality on the linker molecule would be desirable as a Schiff base reaction could form imines with primary amines, a well-known reaction and has previously been used to create dendrimers based on DAB dendrimer scaffolds.[3] 4-Bromomethyl benzonitrile was identified as a potential precursor to a linker molecule due to the presence of a nitrile functionality which can be converted to an aldehyde. Test reduction reactions using a benzonitrile functionalized cyclam, **1**, (Scheme 2.2) however showed no reaction under conditions reported in the literature. [4] Only unreacted starting material was isolated when using DIBAL as reducing agent. The latter has however previously been reported as an effective reducing agent for benzonitriles. [4]



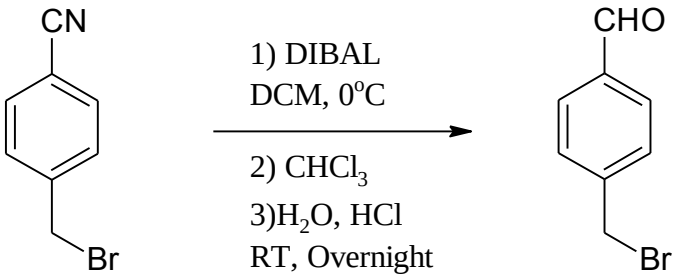
1

Pg= Boc or formamido protecting group

Scheme 2.2: Attempted reduction of benzonitrile functionalized cyclam

A report by Gawley *et al.* showed that the reduction of 4-(bromomethyl) benzonitrile with DIBAL successfully reduced the nitrile functionality to an aldehyde without

reaction occurring at the bromide group (Scheme 2.3).[5] They then reacted this linker molecule with a mono-N- crown ether that was subsequently linked to a fluorophor. We therefore decided to employ this approach in our attempt to obtain benzaldehyde functionalized cyclam. The benzonitrile reduction was thus attempted prior to forming of the cyclam adduct The reaction was performed under argon and was found to yield the product benzaldehyde derivative, **2**, in near quantitative yield.



2

Scheme 2.3: Reduction of 4-(bromomethyl) benzonitrile

Initial characterization was done using FT-IR spectroscopy. The spectrum showed no trace of the band around 2200 cm^{-1} assigned to the nitrile functional group, present in the starting material. A new band is observed at 1692cm^{-1}, which is in the usual range for aromatic aldehyde carbonyls.

Characterization by ^{1}H NMR showed a singlet at 10 ppm which falls within the expected range for an aldehyde proton. The ^{1}H NMR also showed a strong singlet at 4.53 ppm. This resonance is assigned to the methylene protons next to the bromide group (Ar-C**H$_2$**-Br, Scheme 2.3), indicating that the bromide is not reduced during reaction. Characterization by ^{13}C NMR showed a resonance at 191.4 ppm which is assigned as the aldehydic carbonyl (-**C**HO, Scheme 2.3). A resonance at 32 ppm is assigned to the CH_2 group next to the bromide group (-**C**H$_2$-Br, Scheme 2.3). This, along with the ^{1}H NMR data, indicates that the bromine was not reduced under the reaction conditions employed. The analytical data obtained for **2** is in good agreement with that reported by Gawley *et al.* and showed that a successful reaction had taken place.

2.2.3 Mono-functionalization of cyclam

Differentially substituted polyamines are important structural moieties in many pharmaceutical compounds. Many different synthetic methodologies have been developed for both symmetrical and unsymmetrical polyamines.[6] Although some of these reported methodologies are substrate dependent, two basic synthetic strategies exist for the selective modification of amine moieties in polyamines.[6] The first method is based on the selective protection of the substrate followed by modification at the desired chemical center and finally deprotection of the molecule. Another strategy is to use the polyamine in large excess with regards to other reagents. This reaction protocol is a one-pot synthesis of an otherwise synthetically challenging molecule. There are however disadvantages, a mixture of reaction products are often obtained. The use of excess polyamine leads to more chemical waste, which is particularly undesirable if the starting amine is expensive or synthetically difficult to access.

In this project, synthetic strategies based on the use of protecting groups was deemed the most appropriate due to the high cost of cyclam, however several other methods of mono-functionalization were also attempted and are discussed below.

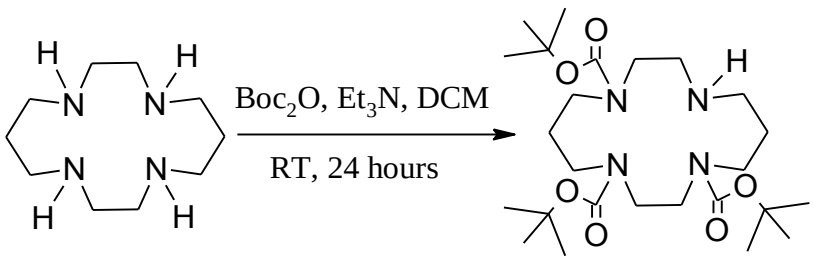
2.2.3.1. Protecting group strategies

Several protecting group strategies for polyamines have previously been reported.[7] Functional groups that have been used as protective groups for amines include tosyl groups [8], carbonate esters (Boc_2O) [9] and formamides [10]. These reactions typically require the direct reaction of the protective group reagent with the polyamine. The cyclic polyamine, cyclam, has four equivalent secondary amine groups. A method is needed to selectively protect three of the four amines, allowing one to remain unprotected for further reaction. Typically such a protection reaction takes place under strictly controlled reaction conditions such as temperature, pH, stoichiometry and concentration. These reactions usually lead to low yields of the desired tri-protected reaction product due to the formation of under and over protected analogues. These reactions therefore require extensive workup procedures such as chromatographic separation (the separation of compounds based on differences in their respective polarities by the use of, for example, a silica gel stationary phase) to obtain the pure tri-protected variant. Literature reports suggest moderate yields of

between 40% - 51% are obtained during the synthesis of tri-tosyl cyclam.[5] The yield of this protection step is fairly low due to the formation of the aforementioned over- and under-protection side products. Furthermore the de-protection reaction conditions for the tri-tosyl cyclam are very harsh and entail refluxing in acetic acid and using HBr. The literature suggests that attempting the synthesis of compounds such as AMD 3100 (JM3100, Chapter 1.7.2, Figure 1.8), an important pharmaceutical compound in the treatment of lymphoma, using tosyl protecting groups can lead to yields of the final product of less than 10%.[8]

2.2.3.2 Tri-protection of cyclam using tertiary butyl carbamates

The use of tertiary-butyl carbamates as protecting group for cyclam was first reported by Guilard *et al*.[9] They reacted 1.8 equivalents of Boc_2O with 1 equivalent of cyclam to form two di-protected cyclam isomers in yields of 39 % and 25% respectively. A by-product of this reaction was the formation of the tri-protected analogue in a yield of 19%. Other authors investigated the use of Boc_2O further in an attempt to maximize the yield of the tri-protected analogue.[10] It was found that performing the reaction with 1 equivalent of cyclam and 2.5- 2.7 equivalents of both the base, usually triethylamine (Et_3N), and the protecting reagent Boc anhydride (Boc_2O), under nitrogen yielded the tri-protected analogue, **3**, as major product. This is shown in Scheme 2.4. The reaction was performed using the reaction protocol reported by Kitagawa *et al*.[10] Chromatographic separation yielded the product as a white highly hygroscopic solid This reaction gave access to the tri-protected derivative in a moderate yield of 62%, comparable to the 70 % yield obtained by Kitagawa *et al*.



3

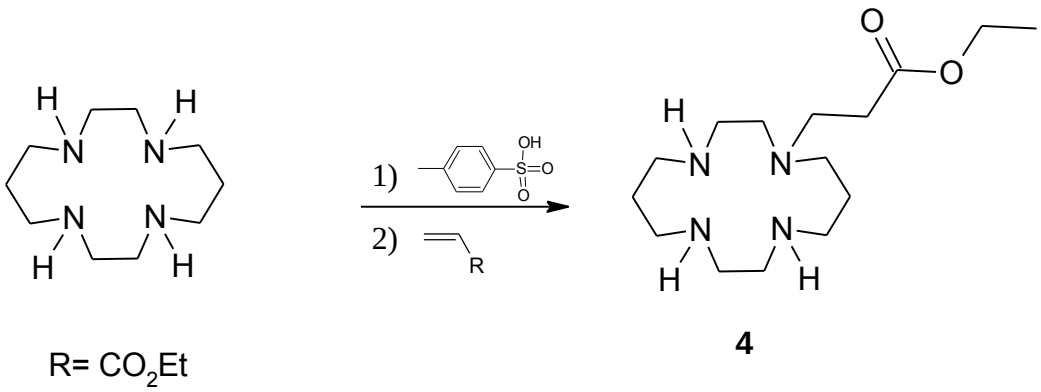
Scheme 2.4: The use of Boc_2O as protecting group in the modification of cyclam

2.2.3.3 Characterization of tri-Boc-cyclam (NMR, FT-IR and MS)

Compound **3**, was initially characterized by Fourier transform infra-red spectroscopy (FT-IR). The spectrum obtained exhibited a very strong band at 1680 cm^{-1} that can be assigned to the carbonyl group of the Boc protected amine. This agrees well with the data reported in the literature. Analysis by ^{1}H NMR spectroscopy showed a more complex spectrum in comparison to the starting cyclam spectrum, due to the loss of symmetry in the molecule. The spectrum shows a strong singlet at 1.44 ppm that integrates for 27 protons. This is assigned the 27 protons of the tertiary butyl groups. The integration of the tertiary butyl groups relative to known cyclam resonances therefore indicates that three Boc protecting groups are present. The compound obtained was also analysed by electrospray ionization mass spectrometry (ESI-MS). The mass spectrum showed a signal at *m/z* 501 which can be assigned to the molecular ion. The obtained analytical data was in good agreement with data reported in the literature.[9]

2.2.3.4 Mono-functionalization through protonation

An alternative synthetic route to the multi-step, protecting group strategy was also investigated. Larpent *et al.* reported a mono-functionalization reaction without protecting groups.[11] The authors described the reaction of 1 equivalent of cyclam with 1 equivalent of para-toluene sulfonic acid (TsOH) and 1 equivalent of a Michael acceptor that yields the mono-N-functionalized cyclam as the major product in yields of between 25 and 81% depending on the Michael acceptor used (Scheme 2.5). These authors speculated that the single equivalent of sulfonic acid protonates the most basic of the four cyclam amines. Reference is made to the pK_a values of cyclam as determined by Hancock *et al*.[12] The pK_a values for cyclam are 11.29, 10.19, 1.61 and 1.91. There is an order of magnitude difference between the two most basic amines and the two least basic amines. Larpent and co-workers reasoned that protonation by a single equivalent of acid occurs at the most basic amine. This leaves only one more highly basic amine that will react preferentially relative to the other two remaining amines. This could be a possible explanation for the observed selectivity towards the mono-N-functionalized product.



R= CO_2Et

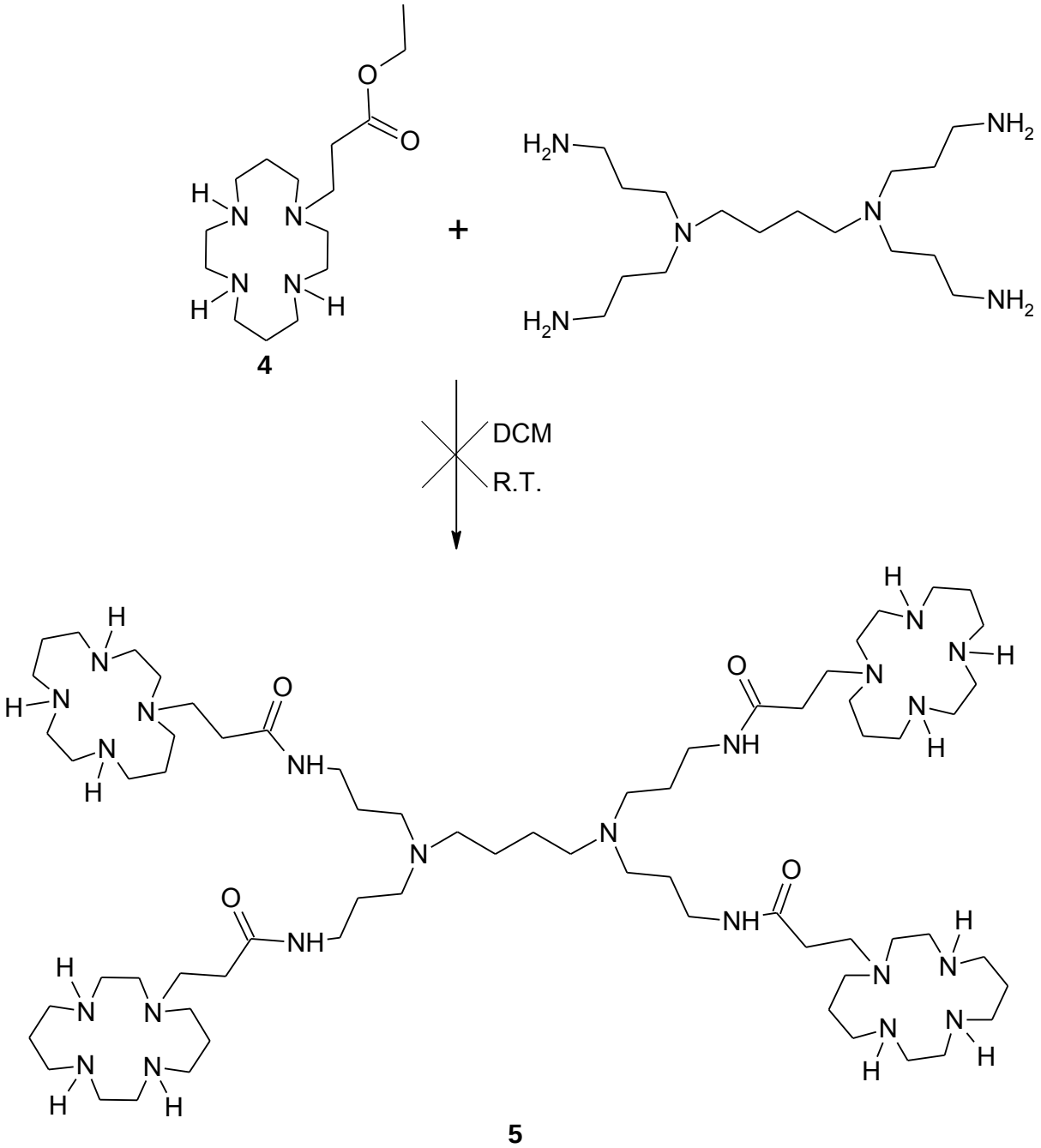
4

Scheme 2.5: Mono-functionalization with a Michael acceptor

Attempted synthesis of **4** was undertaken using the method described by Larpent *et al*.[11] Cyclam was reacted with 1 equivalent each of both the Michael acceptor, ethyl acrylate, and TsOH. The reaction proceeded to yield the mono-functionalized cyclam ester conjugate (**4**) in moderate yield (65 % as reported by Larpent *et al.*) as a white opaque oil after silica gel chromatography. However a problem with the reaction was encountered upon scale up. A significant increase in the amount of multiply functionalized amine is observed and therefore a sharp reduction in the yield of the mono-functionalized product. The crude material requires purification by silica gel chromatography as significant amounts of the di and even small amounts of the tri substituted product forms.

After purification by column chromatography the product **4** was analysed by FT-IR spectroscopy. The IR spectrum showed a large band at 1730 cm^{-1}. This is not present in the spectrum of the starting cyclam. This is indicative of the carbonyl of an ester. Further characterization by ^1H NMR showed more signals when compared to that of the starting cyclam. This is due to the loss of symmetry and consequently a loss of chemical equivalence. A new resonance around 4 ppm is assigned to the protons of the CH_2 group next to the ester functional group (-COOC**H$_2$**CH_3). This signal also integrates for two protons relative to the cyclam protons which indicate successful mono-alkylation. The ^1H NMR also shows that the methine protons of ethyl acrylate disappear due to the successful Michael reaction. Mass spectrometry (ESI-MS) was used to further characterize the product obtained. This showed a signal at *m/z* 301 assigned as the molecular ion of **4**.

Subsequent reaction of the ethyl ester moiety of compound **4** with the primary amine peripheries of the generation 1 DAB dendrimer, as shown in Scheme 2.6, failed to form the required amide functional group necessary for successful immobilization.



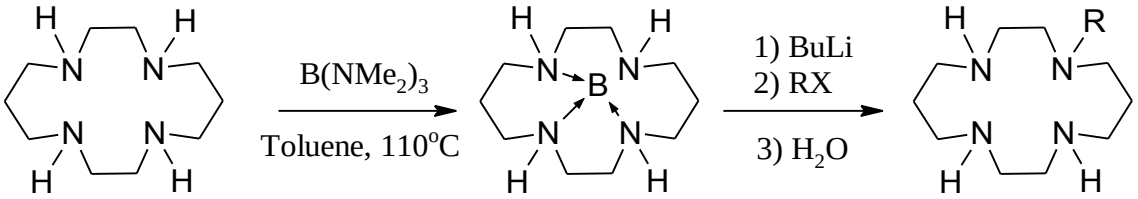
Scheme 2.6: Attempted synthesis of a cyclam-DAB dendrimer conjugate 5 through the formation of amide bonds

Analysis of the crude reaction mixture by FT-IR spectroscopy showed no new bands in the expected C=O amide carbonyl range (amide moiety present in compound **5**). The bands at 1730 cm^{-1} (ester carbonyl of the starting material **4**) and that at 3300 cm^{-1} of the primary amines (of the DAB dendrimer starting material) were also still present in the IR spectrum.

Further analysis by ^{1}H NMR spectroscopy confirmed that only starting material was present in the reaction mixture with resonances observed at 4 ppm assigned as the –COOC**H_2**- protons (due to the ethyl ester moiety of starting material **4**). The ^{1}H NMR spectrum showed a resonance at 2.60 ppm which is also observed in the ^{1}H NMR spectrum of the DAB dendrimer starting material. This resonance is assigned to the -C**H_2**-NH_2 protons of the DAB dendrimer peripheries. No shift is observed for this resonance which indicates that the proposed amide moiety did not form. The use of a different linker molecule was then investigated.

2.2.3.5 Mono-functionalization through boron coordination

Bernard *et al.* reported a mono-N-functionalization reaction of cyclam by temporarily coordinating a boron atom with three of the cyclam secondary amines. [13] This leaves the fourth secondary amine free for further reaction. A transamination is carried out by refluxing tris(dimethylamino) borane with cyclam. This yields the borane intermediate, **6**, with three of the cyclam amines coordinating the boron atom. A nucleophillic substitution reaction was then performed by first reacting the cyclam-boron intermediate with a strong base and then adding the electrophile. These authors tested a range of electrophiles and obtained mono-functionalized cyclam analogues in yields between 70 and 95%.

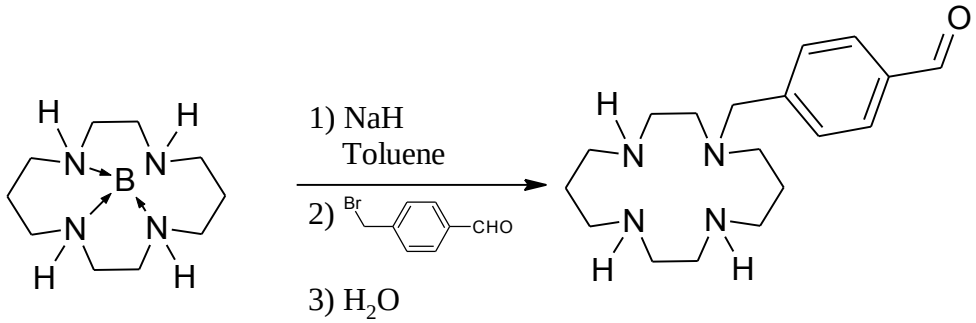


6

Scheme 2.7: Boron coordination followed by mono-functionalization

The main drawback of this reaction is the incompatibility of butyl lithium with certain functional groups. Further investigation of this reaction was performed by Snieckus *et al*.[14] They screened a range of commonly used bases that could potentially serve as an alternative to butyl lithium. It was found that of the bases tested (Et_3N, t-BuONa, DBU, $N(i\text{-}Pr)_2Et$ and NaH) only NaH lead to successful reaction producing some of the mono-N-functionalized cyclams in near quantitative yield. Upon further investigation it was found that this method however fails to deliver good yields when the macrocycle cyclam is replaced by other macrocyles also containing 4 secondary amines, for instance cyclen. This was investigated by Handel *et al*.[15] They found that the reason for this was that in the case of cyclen an autoprotolysis reaction takes place whereby another cyclen molecule acts as base to form a positively charged species, thereby slowing down the transamination reaction with trisdimethyl(amino) borane.

The method described by Handel *et al.* was deemed the most appropriate and was then used in the attempted synthesis of **7** (Scheme 2.8). The boron intermediate was found to be incredibly moisture sensitive leading to the formation of borane gas when exposed to traces of moisture.



6 **7**

Scheme 2.8: Synthesis of a mono-N-functionalized macrocycle via a boron coordinated intermediate

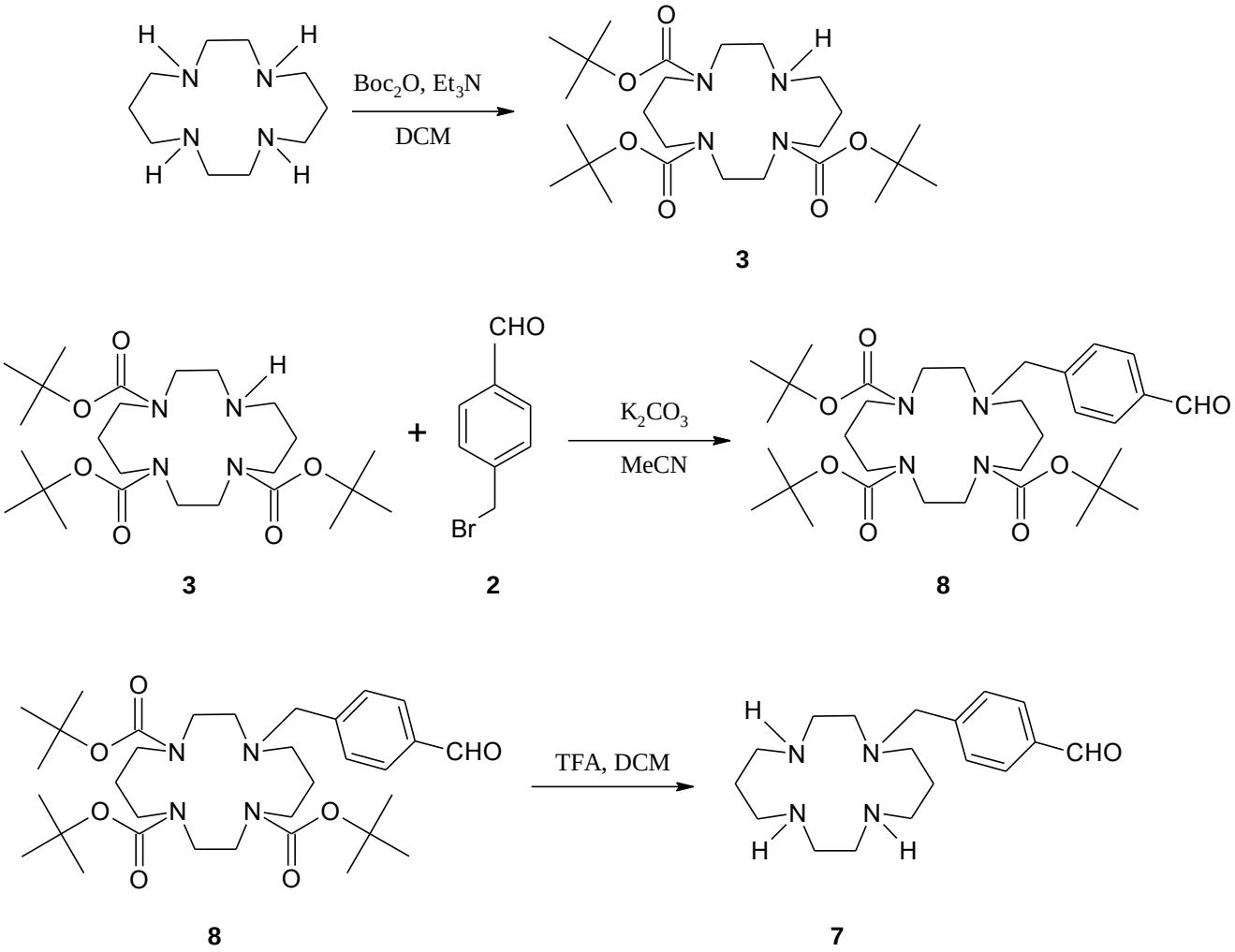
A ^{13}C NMR spectrum of the crude reaction product was recorded after refluxing the trisdimethyl(amino)borane along with cyclam for three hours. Coordination of three of the four amine nitrogens should lead to a loss of symmetry. The ^{13}C NMR spectrum obtained showed 10 carbon resonances due to the loss of symmetry. Further

characterization by mass spectrometry could not be achieved due to the moisture sensitivity of intermediate **6**.

A solution of 4-(bromomethyl) benzaldehyde, **2**, in THF was then added after the first step of the above reaction. The reaction was stirred at room temperature for a further 12 hours. After 12 hours methanol was added to destroy the boron complex. After the solvents were removed under vacuum, the mixture was analysed by thin layer chromatography (TLC). TLC analysis showed the formation of multiple products. These were assigned as the mono-, di-, and tri-substituted derivatives as well as unreacted cyclam. Due to the formation of these over substituted derivatives only very low yields of **7** was obtained after silica gel chromatography. Thus other methods to synthesize compound **7** were explored. The characterization data of compound **7** is presented and discussed in section 2.2.3.7.

2.2.3.6 Further synthetic modification of Boc-protected cyclam **3**

Scheme 2.9 outlines the synthetic modifications attempted to obtain the mono-N-functionalized cyclam.



Scheme 2.9: Synthetic route to mono-N-functionalized cyclams 7 and 8

After tri-protection of cyclam it was reacted with the previously synthesized 4-(bromomethyl) benzaldehyde, **2**. The reaction is performed in the presence of potassium carbonate (K_2CO_3) as base to aid in the nucleophillic substitution of the bromide group by tri-protected cyclam. This proceeded smoothly and yielded compound **8**, as an off-white solid in high yield (88%).

Characterization of compound **8** was done using FT-IR spectroscopy. The IR spectrum shows a weak new band at 1606 cm^{-1}. This can be assigned to the C=C-C

aromatic ring stretch of the benzene moiety in the linker molecule. The FT-IR spectrum of compound **8** does not show the expected carbonyl band at 1696 cm^{-1} band observed in the spectrum of the linker, 4-(bromomethyl) benzaldehyde. This band is masked by the strong and broad carbonyl signal of the Boc groups that is found at 1682 cm^{-1}. The ^{1}H NMR spectrum however shows the expected aldehyde resonance at 9.96 ppm. The signal of the methylene protons originally found at 4.5 ppm in the spectrum of the 4-(bromomethyl) benzaldehyde starting material had shifted upfield to 3.58 ppm in the spectrum of compound **8**. This is indicative of successful nucleophillic substitution of the bromide group by the unprotected amine of cyclam. The product was also analysed by ESI-MS. The mass spectrum showed the molecular ion as the base peak at *m/z* 619 $[M+H]^{+}$.

2.2.3.7 Hydrolysis of Boc-protected amino groups to form compound **7**

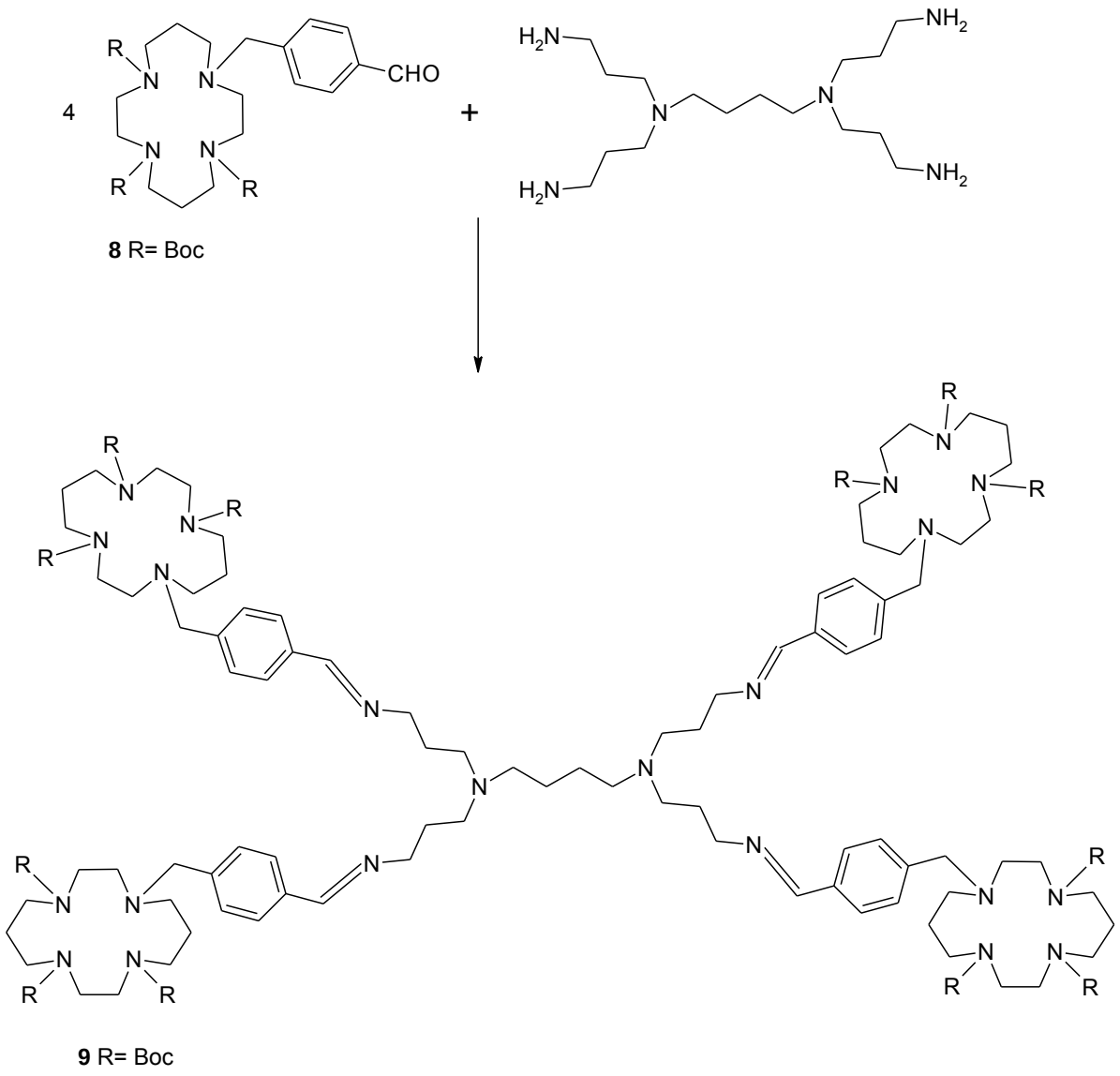
The hydrolysis of the Boc protected amines was accomplished by reaction with trifluoroacetic acid. Reaction conditions analogous to those reported by Benniston *et al* were used.[16] This gave the free amine product in fairly good yield of 80%. Another de-protection reaction that used HCl in methanol instead was also attempted but gave lower yields of the final product.

The FT-IR spectrum of compound **7** showed a new band at 3300 cm^{-1} indicative of the N-H stretch of an amine. The band around 1690 cm^{-1} was found to have decreased in intensity. Unfortunately the C=O stretching frequency of the aldehyde and that of the Boc groups of the starting material overlap. Thus it is difficult to ascertain using FT-IR spectroscopy whether de-protection was successful. However, a ^{1}H NMR spectrum of the product does not show a resonance at 1.40 ppm normally assigned to the 27 protons of the tertiary butyl groups of Boc. This indicates successful hydrolysis of the Boc protected amines.

2.2.4 Attempted synthesis of a macrocycle-dendrimer conjugate

The aldehyde functionalized cyclam **8** was reacted with the peripheral functionalities of commercially available polypropylenimine tetramine dendrimer (DAB–Am-4). The primary amines on the dendrimer surface react with the aldehyde group of **8** to form

imine bonds thus anchoring the macrocycle cyclam molecules to the periphery of the DAB dendrimer to form compound **9**. This is shown in Scheme 2.10.



Scheme 2.10: Attempted synthesis of a dendrimer with macrocycle peripheries

The reaction was monitored by FT-IR spectroscopy. A new band at 1644 cm^{-1} was observed and is assigned as the C=N stretch. The reaction was stopped after 48 hours and the reaction product precipitated using a mixture of DCM and ether which yielded a light yellow powder. A ^{1}H NMR spectrum of the reaction product showed a singlet resonance at 8.26 ppm which is assigned as the imine proton resonance (-

HC=N-). No trace of any unreacted aldehyde remained. The resonances associated with the cyclam macrocycles are observed at 1.68 (broad, N-CH_2-C**H_2**-CH_2-N), 2.46(broad, -C**H_2**-N-) and 2.62 ppm (broad, -C**H_2**-N). Furthermore a triplet is observed at 3.62 ppm which is assigned as the methylene protons of the DAB dendrimer scaffold next to the imine group (-C**H_2**-N=CH-, in the product). This resonance is shifted downfield in the product spectrum (3.62 ppm) when compared to the DAB dendrimer starting material's spectrum (2.70 ppm). This downfield shift as well as the resonance observed at 8.26 ppm confirms that imine formation had taken place to yield compound **9**.

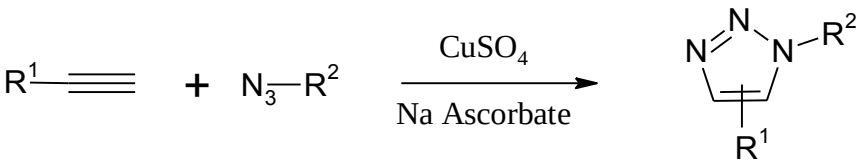
The de-protection reaction of the cyclam amines utilizing a mixture of TFA and DCM was then attempted. This reaction was once again monitored by FT-IR, after six hours, three signals were observed above 3250 cm^{-1}. These bands were assigned as the single N-H stretch of a secondary amine as well as the two stretches of a primary amine. A ^{1}H NMR spectrum on the crude reaction mixture showed a resonance at 9.90 ppm which is an aldehyde resonance and indicates that hydrolysis took place under the conditions employed. Other authors have also observed the hydrolysis of imine bonds under these conditions.[17, 18] Due to the problems encountered with the deprotection of the cyclam units in compound **9** we did not pursue this approach any further.

2.3 Synthesis of a benzene cored "click" dendrimer

The term "click chemistry" refers to a group of reactions that mimics nature by joining together small molecules through a heteroatom reliably and in high yield.[19] Reactions identified as "click reactions" should operate under benign conditions, be selective and tolerant towards functional groups. Finally, reactions classified as click reactions should provide easy workup methods that ideally involves non chromatographic product isolation.[19]

The azide-alkyne Huisgens 1,3 cycloaddition reaction (Shown in Scheme 2.11) is a click reaction that links two molecules together through the cycloaddition reaction of an azide with an alkyne to form a substituted triazole. Reactions of this type have

been employed by Sharpless and co-workers to synthesize a range of substituted triazoles and are often employed in the pharmaceutical industry.[20,]



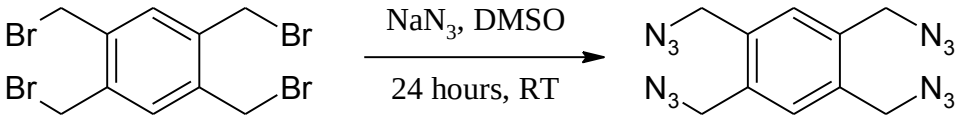
Scheme 2.11: A typical (Huisgens cycloaddition) click reaction

The reaction is catalysed by different metal salts with copper and ruthenium most commonly used. The copper catalysed reaction yields a 1,4 disubstituted triazole while the ruthenium catalysed reaction yields the 1,5 disubstituted triazole product.

Click reactions using cyclam have been reported before. For example these cyclam based triazole systems have been used to construct chemical sensors for zinc.[21] We thus set out to prepare a cyclam-dendrimer conjugate with a triazole linker using standard click chemistry. The approach adopted was to first prepare an azide functionalized core and to react this with an alkyne functionalized cyclam species.

2.3.1 Synthesis of tetra-azide functionalized dendrimer core **10**

The tetra-azide functionalized dendrimer core was synthesized by nucleophillic substitution reaction of tetrakis (bromomethyl) benzene with sodium azide through the method reported by Alvarez *et al.* as shown in Scheme 2.12.[22] This formed the tetrakis(azidomethyl)benzene derivative in near quantitative yield.



10

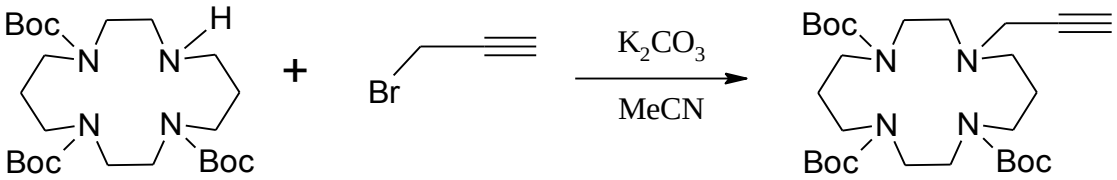
Scheme 2.12: Synthesis of an azide functionalized dendrimer core 10

The characterization of azides by IR was studied by Lieber *et al*.[23] They summarized that azides have a strong asymmetric N≡N stretch in the range of 2167 – 2080 cm^{-1}.

A second weaker symmetric N≡N stretch is also observed usually in the range of 1343 to 1177 cm^{-1}. A FT-IR spectrum of compound **10** showed a strong band around 2086 cm^{-1}(asymmetric N≡N) and a band at 1242 cm^{-1} which can therefore be assigned as the symmetric N≡N. Further characterization was done by ^{1}H NMR spectroscopy. Two resonances are observed. A singlet resonance at 4.47 ppm is assigned to the protons of the methylene group next to the azide group. Another singlet is observed at 7.40 ppm. This is due to the aromatic protons.

2.3.2 Synthesis and charaterization of alkyne functionalized cyclam **11**

A terminal alkyne functional group is required for the cycloaddition reaction. Tamanini *et al* reported the synthesis of click generated cyclam based zinc sensors.[21] Using the procedure of Tamanini *et al.* the cyclam derivative **11** was synthesized in a simple nucleophillic substitution reaction with propargyl bromide in the presence of K_2CO_3 as base (Scheme 2.13) and isolated as a white solid in high yields (79%).



3 **11**

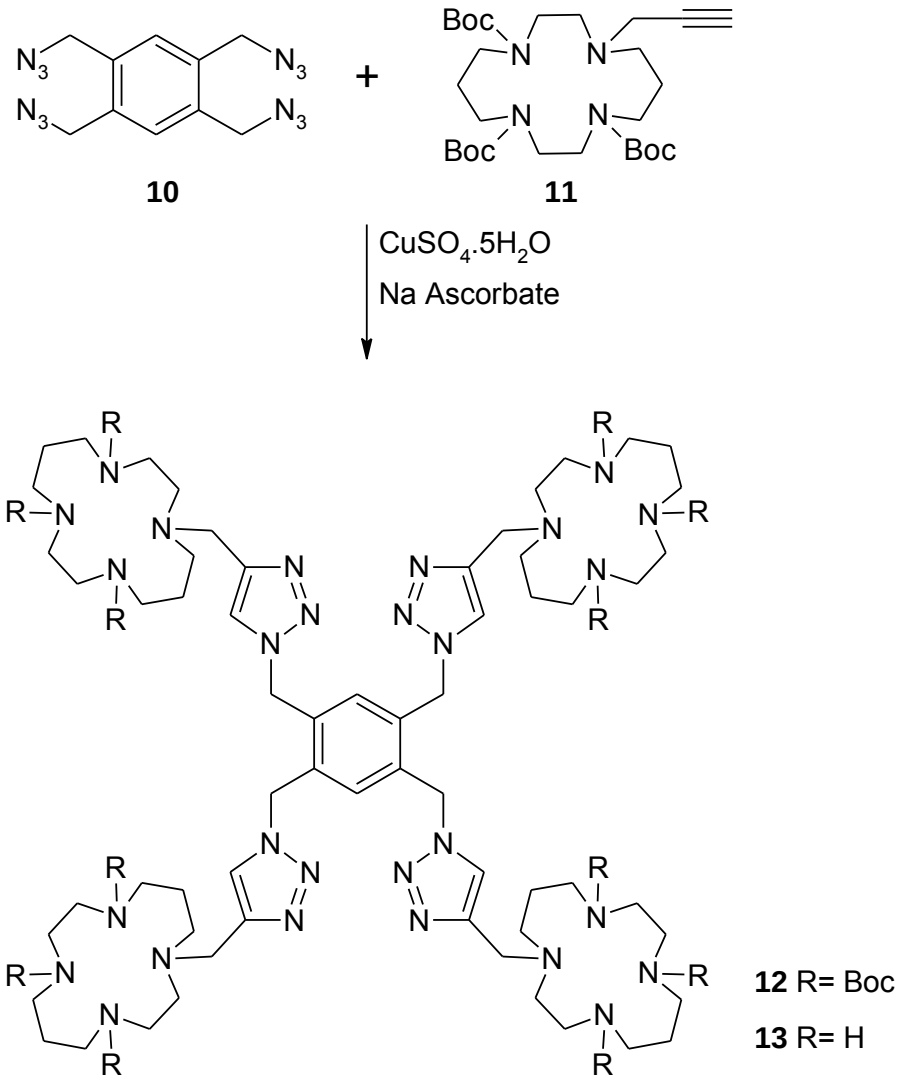
Scheme 2.13: Synthesis of the alkyne functionalized macrocycle 11

The obtained product was analysed by FT-IR, ^{1}H NMR and ^{13}C NMR spectroscopy as well as ESI-MS. The ^{1}H NMR spectrum showed the expected signals for the alkyne group, a singlet resonance at 2.14 ppm (-C≡C**H**). A signal at 3.36 ppm is assigned as the deshielded methylene group next to the alkyne (-C$\mathbf{H_2}$-C≡CH). The ^{13}C NMR spectrum showed resonances at 73.2 and 77.5 which are assigned as the terminal alkyne carbon and the internal alkyne carbon respectively. Characterization by ESI-MS showed the molecular ion $[M+H]^+$ as the base peak. The obtained characterization data was in good agreement with that obtained by Tamanini *et al*.[21]

2.3.3 Cycloaddition reaction of azide dendrimer core and alkyne functionalized macrocycle

With the aromatic azide core, compound **10**, as well as the alkyne functionalized cyclam, compound **11**, in hand the cycloaddition reaction (Huisgens 1,3 cycloaddition) was attempted. However, deprotection of the cyclam amines (hydrolysis of the Boc-protected amines) is also necessary. This could be done either before or after the cycloaddition reaction. Deprotection prior to the coupling reaction was found not to be a feasible approach. The de-protected cyclam-alkyne derivative does not undergo the click reaction, most likely due to coordination between cyclam and the Cu(II) ions used as a catalyst. This observation agrees with what has been found by other researchers.[19] Two possible solutions to this problem exist. The first is to react the alkyne functionalized protected-macrocycle with the dendrimer core. Another solution is to use a slight excess of $CuSO_4$ thereby forming the cyclam copper complex with the excess copper available to catalyse the cycloaddition reaction.

We opted to use the first approach. The synthesized reaction partners **10** and **11** were stirred in THF at room temperature along with catalytic amounts of $CuSO_4$ and sodium ascorbate as oxidant (shown in Scheme 2.14). The reaction product was characterized by ^{1}H NMR, ^{13}C NMR and FT-IR spectroscopy. The ^{1}H NMR spectrum obtained showed that the methylene resonance (Ar-C**H$_2$**-triazole in **12**) had shifted downfield from 4.47 ppm observed for tetrakis(azidomethyl)benzene (**10**) to 5.60 ppm (singlet, 8 protons by integration) in the product spectrum. A new resonance is also observed at 7.50 ppm (singlet, 4 protons by integration) which is assigned as the protons of the formed triazole groups. Further characterization by ^{13}C NMR showed the expected triazole carbon resonances that are usually observed at 120 and 130 ppm.[24] Compound **12** underwent fragmentation under ESI-MS conditions. The mass spectrum showed fragments consisting of the benzene core with one or more traizole groups as well as tri-protected cyclam. The obtained characterization data for **12** is in good agreement with characterization data of similar compounds in the literature.[25, 26]



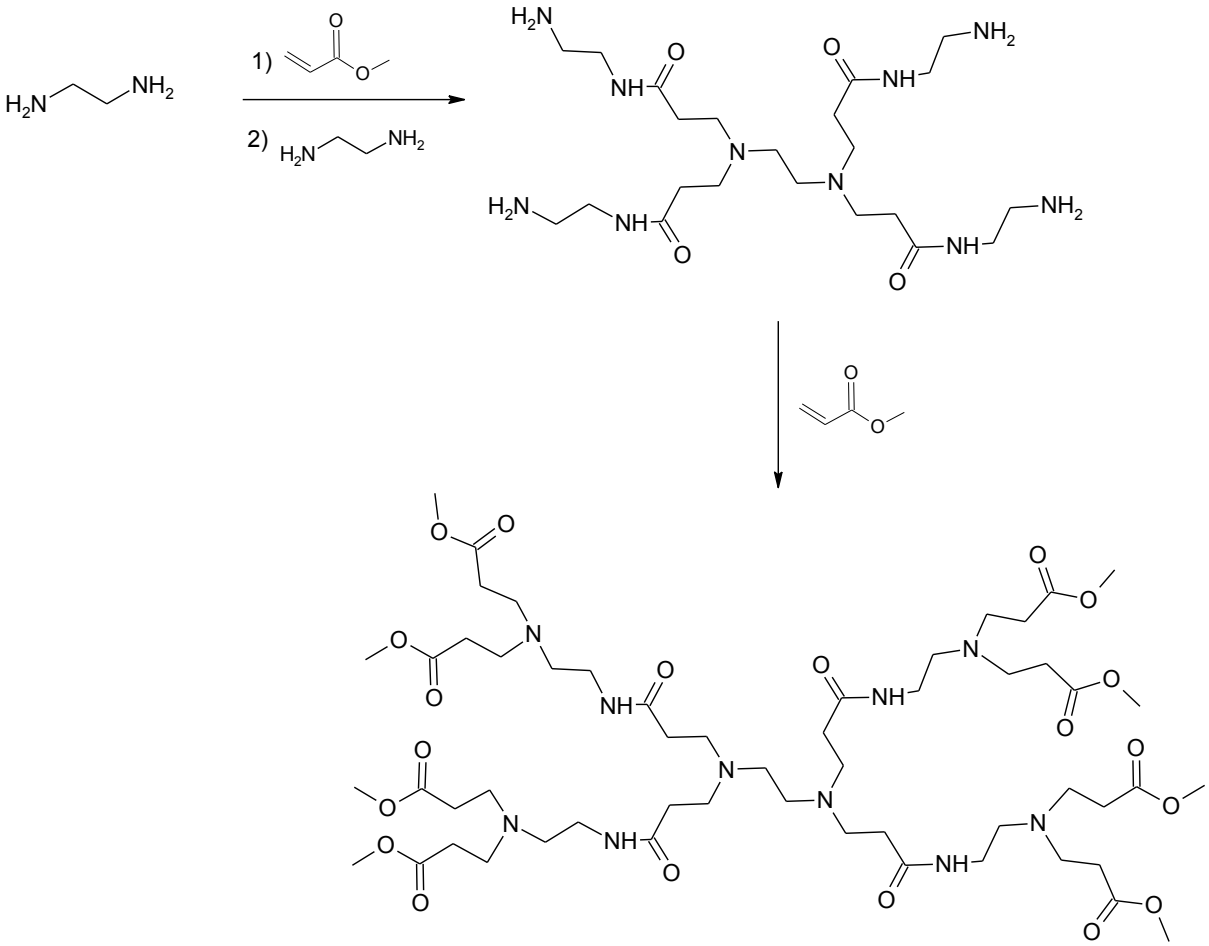
Scheme 2.14: Cycloaddition click reaction

With compound **12** in hand we then attempted the de-protection of the cyclam units. Compound **12** was thus subjected to deprotection reaction conditions in an attempt to synthesize **13**. Utilizing a mixture of HCl/MeOH or TFA/DCM as deprotecting agents, the reaction was found not to go to completion. The relevant Boc C=O stretches are still observed in the FT-IR spectrum and the corresponding resonances are also observed in the ^{1}H and ^{13}C NMR spectra of products isolated. The reaction therefore yields a complex mixture of products containing species with one or more Boc protected amines. Similar problems were reported by others using related systems. Literature reports indicate that often complex workup procedures requiring, amongst others, HPLC and GPC separations are necessary.[26, 27] In addition reported yields of compounds containing these envisaged moieties were reported to be

relatively low.[26] Due to these factors attempts at further purification and modification of **13** were abandoned.

2.4 Cyclam cored PAMAM type dendrimers

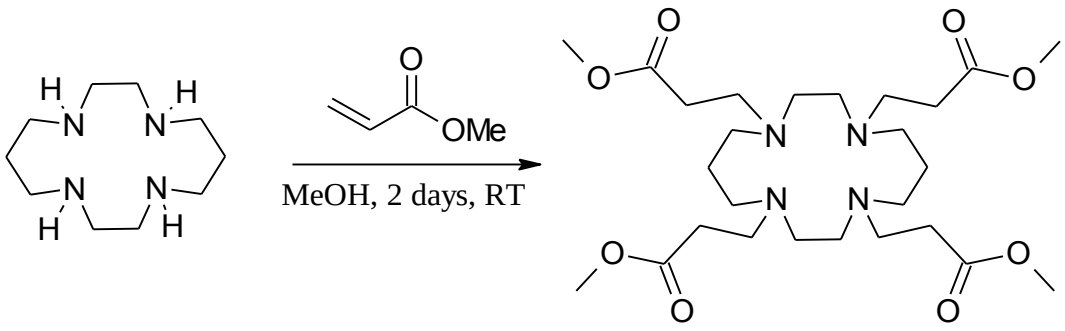
Starburst polyamidoamine dendrimers were some of the first dendrimers successfully synthesized, characterized and commercialized.[28] PAMAM dendrimers are usually synthesized by the divergent method starting with a nucleophillic core such as a multivalent amine. The dendrimer is synthesized by sequentially reacting the core (or a lower dendrimer generation) with a Michael acceptor (methyl acrylate in Scheme 2.15) and then performing an amidation reaction (the scheme shows the use of ethylenediamine to perform the amidation reaction). Generation growth occurs through an iterative sequence of Michael addition reactions followed by amidation reactions.



Scheme 2.15: Synthesis of a PAMAM dendrimer based on an ethylenediamine core

2.4.1 Synthesis and characterization of dendrimer core **14**

Drawing inspiration from this synthetic methodology, a dendrimer with cyclam as its core was envisaged. The same general generation growth reactions discussed above was employed in an attempt to synthesize a cyclam-cored dendrimer. The first reaction in this divergent synthesis is the Michael addition reaction of cyclam (Michael donor) using a large excess of the Michael acceptor, methyl acrylate (methyl prop-2-enoate). The reaction was performed using a method reported by Subik *et al*.[29] The reaction (as shown in Scheme 2.16) is performed under argon at room temperature and yields the product in good yield (82%) after chromatographic purification to remove the invariably formed mono, di and tri-Michael addition products.



14

Scheme 2.16: Synthesis of the growing dendrimer core 14

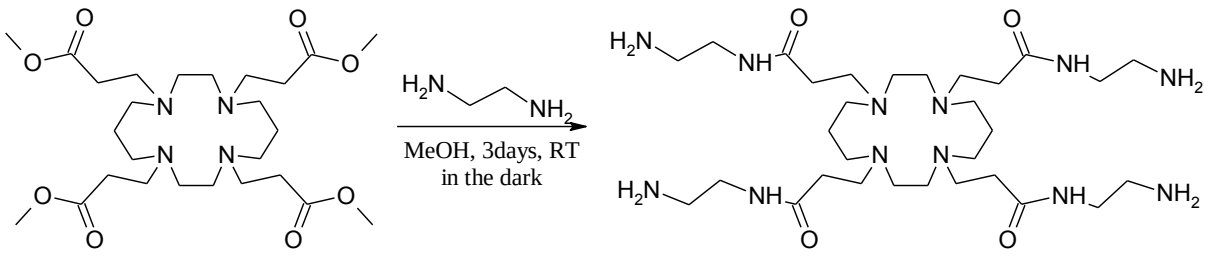
Compound **14** was initially characterized by FT-IR spectroscopy. The sharp absorption around 3300 cm^{-1} previously assigned as the N-H stretch present in the starting cyclam is no longer observed. A new band around 1730 cm^{-1} is observed and is assigned as the carbonyl of an ester functional group. Further characterization was accomplished by ^{1}H NMR spectroscopy. The resonance of the methoxy protons were observed at 3.67 ppm. Integration of these protons indicated that 12 methoxy protons were present. The ^{13}C NMR spectrum showed a resonance at 173.2 ppm, which is assigned as the carbon of the ester moiety, which indicates that the reaction had successfully taken place. An ESI-MS of **14** showed a signal at *m/z* 545 which is assigned as the molecular ion. The characterization data was in good agreement with that reported by Subik *et al*.[29]

The product of this reaction, **14**, is then further reacted in an amidation reaction with ethylene diamine to form the tetra-amide derivative with free amines at the periphery of the growing dendrimer.

2.4.2 Amidation reaction performed on growing dendrimer

Compound **14** was subsequently treated with a large excess of ethylene diamine (10 equivalents) as shown in Scheme 2.17. No crosslinking of between two molecules of compound **15** is observed due to the large excess of ethylene diamine used and the further dilution of the reaction by using methanol as solvent. The solution was stirred

at room temperature for 3 days which gave the product **15** in good yield (81%) as a light yellow solid after workup.



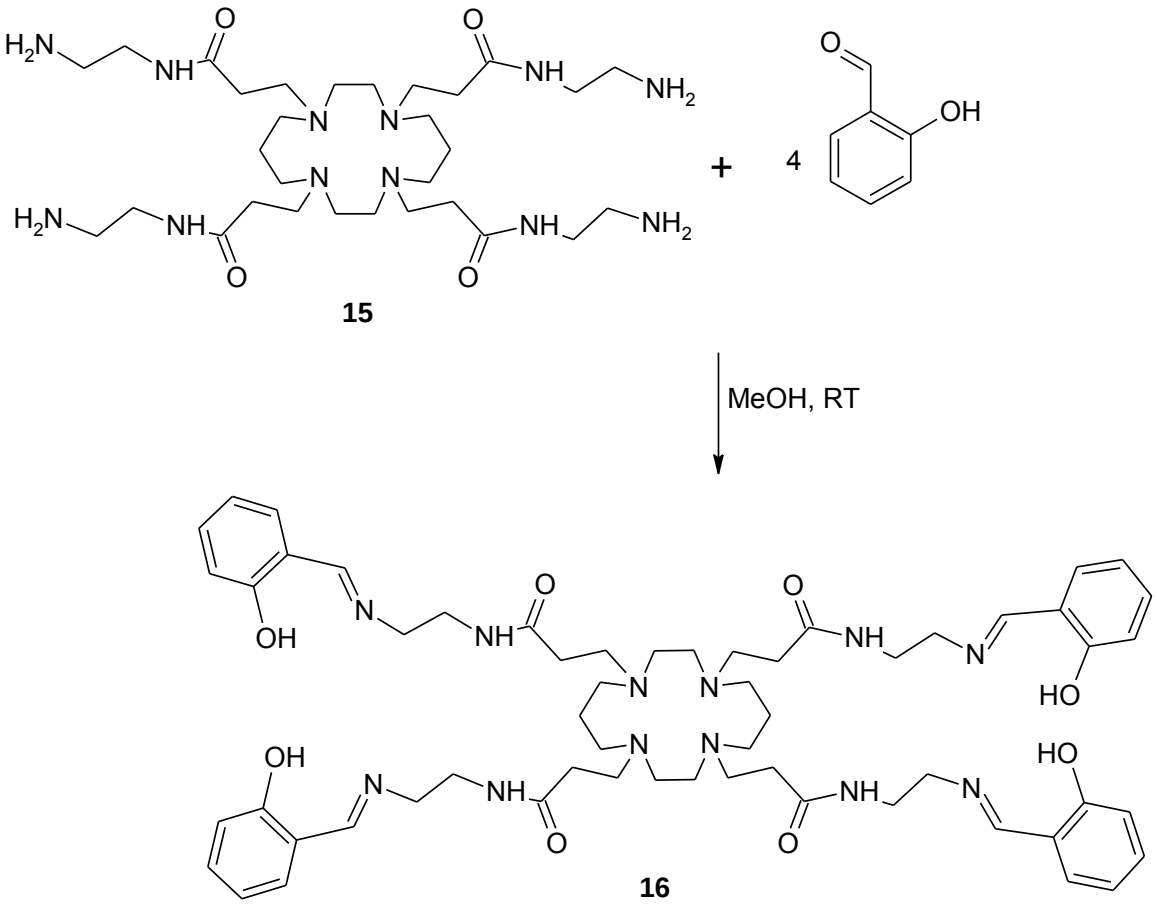
14 **15**

Scheme 2.17: Amidation reaction performed on 14

Characterization of the product, **15**, using IR spectroscopy showed that the carbonyl band had shifted to lower wavenumbers. The carbonyl band now appears at 1627 cm^{-1}. This is within the region that amide carbonyls typically absorb. Furthermore a sharp peak at 1620 cm^{-1} is observed and this was assigned to the primary amine. A ^{1}H NMR spectrum was recorded. The resonance of the methoxy protons present in the starting material was no longer observed. The expected resonance of the -C**H$_2$**-NH_2 and -C**H$_2$**-NHCO- groups are observed close to the resonances of the cyclam core protons. A ^{13}C NMR spectrum of the material obtained showed that the carbonyl resonance had shifted from 172.3 to 170.1 ppm indicative of amide formation. The mass spectrum showed a signal at m/z 657 which is assigned as the molecular ion of **15**.

2.4.3 Synthesis of cyclam cored dendrimer with salicylaldimine peripheries **16**

After purification compound **15** is reacted in a Schiff base reaction with salicyladehyde to form an imine bond between the aldehyde moiety of salicylaldehyde and the amine periphery (Scheme 2.18). This yielded the final dendrimer structure bearing salicylaldimine peripheries as shown below.



15

16

Scheme 2.18: Schiff base condensation between the growing macrocyclic dendrimer core and salicylaldehyde to yield 16

This forms the novel cyclam cored dendrimer with salicylaldimine peripheries, **16**. The product is isolated as a stable yellow solid in 73% yield.

Characterisation by FT-IR spectroscopy showed a new band at 1627 cm^{-1} indicative of imine bond formation, no trace of the starting aldehyde carbonyl of salicylaldehyde remains after workup.

The ^{1}H NMR spectrum of salicylaldehyde (reactant) shows a singlet at 10 ppm. This singlet at 10 ppm was not observed in the spectrum of the product, **16** (Figure 2.3), however an upfield shifted singlet at 8.3 ppm was observed. This resonance does not appear in the ^{1}H NMR spectra of either of the starting materials. The resonance is in the expected imine proton range and integrates for 4 protons. A broad singlet resonance is also observed far downfield at 13.24 ppm. This resonance is assigned as the O-**H** protons of the salicylaldimine periphery. The aromatic protons (16H

aromatic protons in total) lead to resonances between 6.85 and 7.80 ppm as is expected.

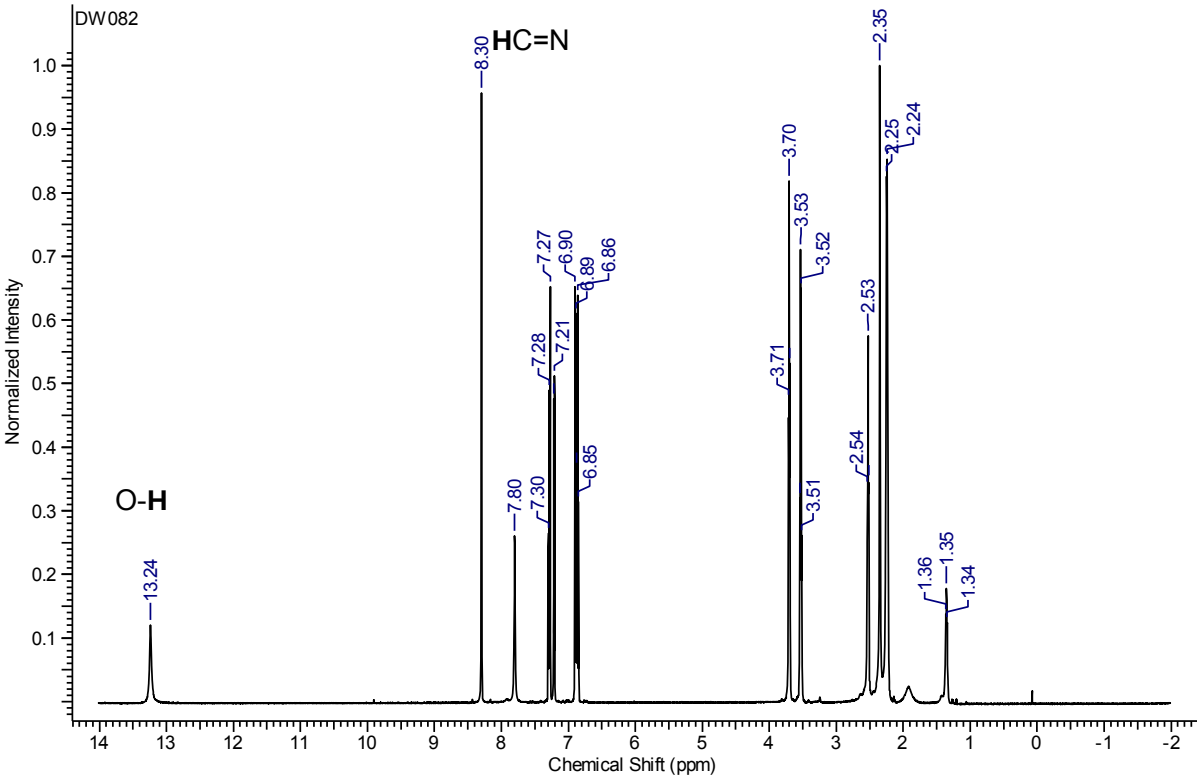


Figure 2.3: ^{1}H NMR spectrum of compound 16

Further characterization was carried out by ^{13}C NMR spectroscopy. The ^{13}C NMR spectrum (Figure 2.4) shows three resonances downfield from the other resonances. The most downfield resonance at 172.7 ppm also appears in the ^{13}C NMR spectrum of the starting material and has previously been assigned as the resonance of the deshielded amide carbon (N**C**=O). The resonance at 166.4 ppm is due to the resonance of an aromatic carbon bearing an O-H group while the imine carbon resonates at 161 ppm.

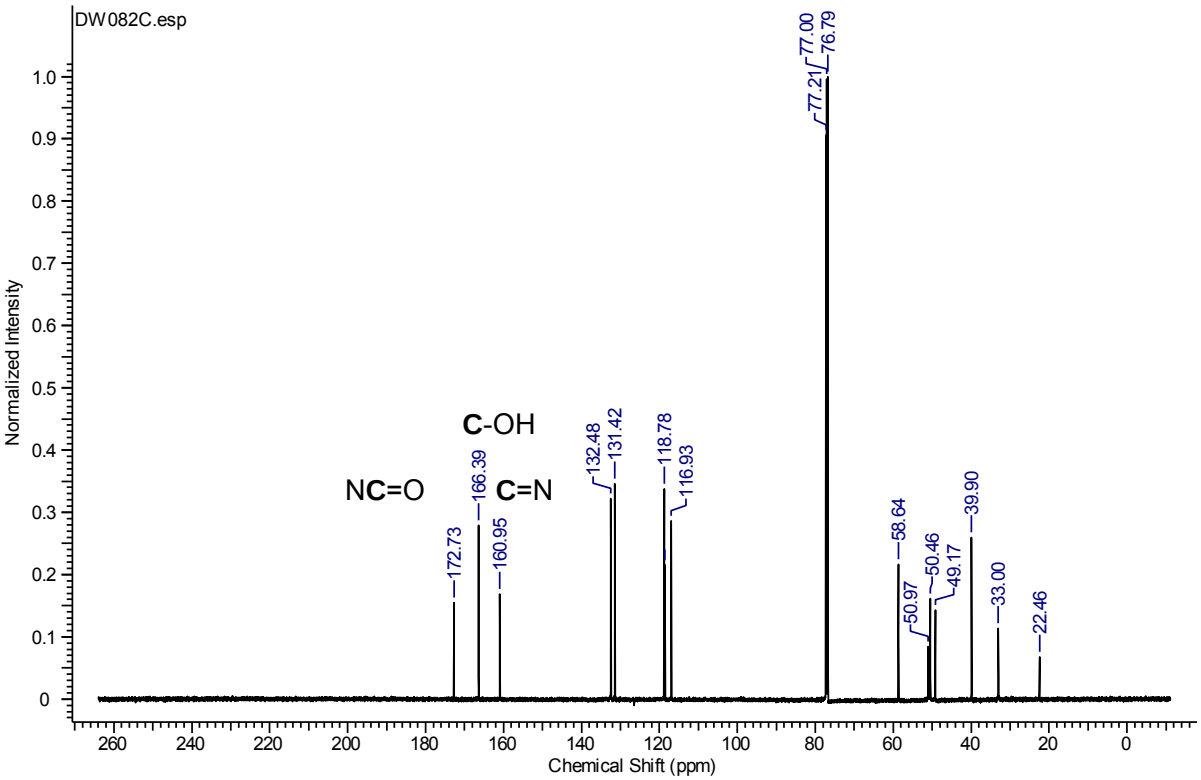


Figure 2.4: ^{13}C NMR spectrum of compound 16

The mass spectrum of **16** showed a signal at *m/z* 1074 which is assigned as the molecular ion. Furthermore the doubly charged molecular ion is observed at *m/z* 537.

2.5 Conclusions

Mono-functionalized Boc protected derivatives of cyclam were prepared successfully including a cyclam with an ester pendant arm as well as a benzaldehyde functionalized cyclam. The ester functionalized cyclam failed to react with the peripheries of the DAB-$(NH_2)_4$ dendrimer core while the synthesis of mono benzaldehyde functionalized cyclam suffered from low yields. An alternative approach was then attempted which consisted of first anchoring the benzaldehyde functionalized tri-Boc protected cyclam derivative **8** to the periphery of the generation 1 DAB-$(NH_2)_4$ dendrimer through the formation of imine bonds to form a macrocycle-dendrimer conjugate. However when attempting to deprotect the DAB cored dendrimer, hydrolysis of the imine bonds take place, leading to detachment of the cyclam units from the dendrimer periphery.

Compound **12**, a benzene cored dendrimer with cyclam peripheries linked via triazole units, was successfully synthesized using click chemistry by first synthesizing the tetra azide functionalized aromatic core (**10**) and a alkyne functionalized cyclam (**11**). However, once again deprotection of the Boc protected cyclam units in compound **12** was not successful and yielded a complex mixture of products.

The synthesis of **16**, a cyclam cored dendrimer with salicylaldimine peripheries, was successful. Compound **16** was synthesized by utilizing Michael addition and amidation reactions followed by a Schiff base condensation reaction with salicylaldehyde to yield the final product: a macrocycle-dendrimer conjugate.

2.6 Experimental section

General methods and materials

All reagents were obtained from either Merck or Sigma Aldrich and used without any further purification. Solvents were obtained from Merck or Kimix and dried by distilling over the appropriate drying agents. The solvents THF, toluene and hexane were dried by distillation over sodium wire while DCM and acetonitrile were dried by distillation over phosphorous pentoxide. Ethanol and methanol were dried by distillation over a mixture of magnesium filings and iodine.

Reactions were performed using standard Schlenk techniques under an inert atmosphere of nitrogen gas unless otherwise stated.

FT-IR spectra were recorded on a Thermo Nicolet Avatar 330 FT-IR spectrometer with a Smart Performer (Zn/Se) ATR attachment. NMR spectra were recorded using a Varian Unity Inova NMR spectrometer. Mass spectra were recorded on a Waters Synapt G2 spectrometer.

Synthesis of 4-(bromomethyl)benzaldehyde (2)

A Schlenk tube was charged with 4-(bromomethyl)benzonitrile (0.200 g, 1.00 mmol). The reaction vessel was evacuated and refilled with argon gas three times. Dry toluene (2.5ml) was added via syringe and the resulting colourless solution cooled to 0°C. Diisobutylalluminium hydride (1.5 ml, 1M in toluene) was then added dropwise via syringe. The mixture turned faintly yellow. The reaction mixture was stirred at 0°C for one hour. Chloroform (4ml) was then slowly added followed by a dilute HCl solution (3ml of a 1M solution) and stirred overnight (15 hours). The mixture was extracted with chloroform (2 x 20 ml) and the combined organic phase dried over anhydrous $MgSO_4$. The organic phase was filtered and the solvent removed under reduced pressure. The crude, off white, material was then dissolved in a mixture of DCM/Hexane (2:3 by volume) and purified with silica gel chromatography using the same solvent mixture as the eluent. This yielded the product as white flakes (0.194 g, 96%). Mp 98-100°C; R_f=0.17 (DCM/Hexane, 2:3); IR (ATR) υ = 1692, 1603 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H 4.53 (s, 2H, -C**H**$_2$-Br) 7.55 (d, 2H, $^3J_{H-H}$ 8.36Hz, Ar-**H**), 7.86 (d, 2H, $^3J_{H-H}$ 8.36Hz, Ar-**H**), 10.03 ppm (s, 1H, C**H**O); ^{13}C NMR (75MHz, $CDCl_3$) δ_C 31.9 (Br-**C**H_2-), 129.4 (Ar), 129.6 (Ar), 130.1 (Ar), 136.1 (Ar), 144.2 (Ar), 191.4 ppm (-**C**HO); MS (ESI) *m/z*: 200 $[M+H]^+$.

Synthesis of 1,4,8-tris(tert-butoxycarbonyl)-1,4,8,11-tetraazacyclotetradecane (3)

Cyclam (0.200g, 0.998 mmol) and triethyl amine (0.278g, 2.75 mmol) were dissolved in DCM (10ml.). A solution of di-tert-butyl dicarbonate (0.577 g, 2.64 mmol) in DCM (5ml) was then added to the reaction, via syringe, over a period of 30 minutes. The reaction mixture was stirred at room temperature under N_2 for 24 hours. The solvent was then removed under reduced pressure to yield a colourless oil. The crude material was dissolved in a small amount of DCM/MeOH (95:5 by volume) and purified by silica gel chromatography using the same solvent mixture as the eluent. This yielded a white oil as the product. (Yield: 0.309 g, 62%) R_f= 0.2 (DCM/MeOH, 95:5); IR (ATR) : υ = 1682 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H 1.44 (s, 27H, C(C**H**$_3$)$_3$) 1.69 (m, 2H, -C**H**$_2$-CH_2-N-), 1.91 (m, 2H, -C**H**$_2$-CH_2-N-), 2.60 (t, 2H, $^3J_{H-H}$ 5.58 Hz, -

CH_2-C**H$_2$**-NH-) 2.77 (t, 2H, $^3J_{H-H}$ 5.14 Hz, -N-CH_2-C**H$_2$**-NH-) 3.26 -3.38 ppm (m, 12H, -C**H$_2$**-N-);^{13}C NMR (75 MHz, $CDCl_3$) δ_c: 21.1, (-CH_2-**C**H_2-CH_2-N-) 23.1 (**C**H_2-CH_2-N-), 28.2 (-C(**C**H_3)$_3$), 43.8 (-**C**H_2-NH-), 45.6 (-**C**H_2-NH-), 46.4 (-CH_2-**C**H_2-N-), 46.8 (-CH_2-**C**H_2-N-), 47.4 (-CH_2-**C**H_2-N-), 49.7 (-N-**C**H_2-CH_2-N-), 50.3 (-N-**C**H_2-CH_2-N-), 53.2 (-N-**C**H_2-CH_2-NH-) 79.1 (-**C**$(CH_3)_3$), 155.1 ppm (-**C**OO-); MS (ESI) *m/z*: 501 $[M+H]^+$.

Synthesis of 3-(1,4,8,11-tetraazacyclotetradecan-1-yl)propionic acid ethyl ester (4)

Cyclam (0.200 g, 0.998 mmol) was dissolved in chloroform (4 ml). *Para*-toluene sulfonic acid monohydrate (190 mg, 1.00 mmol) was then added to the solution as a solid. Ethyl acrylate (1.0 mmol, 0.11 ml) was added via syringe. The reaction mixture was stirred for 18 hours at room temperature. After 18 hours the reaction mixture was concentrated under reduced pressure and loaded onto a silica gel column. The product was obtained by eluting with the solvent mixture $CHCl_3$: MeOH: Et_3N (10 :1 :1 by volume). This yielded the product as an opaque colourless oil, in 60 % yield (180 mg). R_f= 0.68 ($CHCl_3$/ MeOH/Et_3N, 10: 1: 1); IR (ATR) υ = 1730 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 1.21 (t, $^3J_{H-H}$ 7.2 Hz, -C**H$_3$**), 1.60-1.80 (m, 4H, -N-CH_2-C**H$_2$**-CH_2-N-), 2.45, 2.47-2.75 (m, 16H, -C**H$_2$**-N-), 2.80 (t, 2H, $^3J_{H-H}$, -C**H$_2$**-N-), 4.09 (q, 2H, $^3J_{H-H}$ 7.2 Hz -COO-**C**H_2-); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 14.2 (-COO-CH_2-**C**H_3), 22.2 (-N-CH_2-**C**H_2-CH_2-N-), 22.3 (-N-CH_2-**C**H_2-CH_2-N-), 32.4 (-**C**H_2-COO-CH_3), 42.2 (-N-**C**H_2-**C**H_2-N-), 43.6 (-N-**C**H_2-CH_2-**C**H_2-N-); 48.6 (-CH_2-N-), 48.8 (-CH_2-N-), 52.2 (-N-**C**H_2-CH2-COO-) 60.2 (-COO-**C**H_2-), 172.2 ppm (-**C**OO-); MS (ESI): m/z 301 $[M+H]^+$

Synthesis of boron-cyclam (6)

Cyclam (0.998 mmol, 200 mg) was dissolved in toluene (15 ml) and kept under argon. Tris(dimethylamino) borane (1.00 mmol, 190 µl) was added via syringe. The reaction mixture was stirred under argon for 5 hours at reflux. After 5 hours a sample of the reaction mixture was transferred into an NMR tube under the flow of argon. A sealed capillary filled with D_2O was then added to the NMR tube and the tube sealed.

^{13}C NMR (Toluene, 75 MHz) δ_C 30.5 (-CH_2-**C**H_2-CH_2-N-), 33.6 (-CH_2-**C**H_2-CH_2-N-), 46.1 (-N-**C**H_2-CH_2-N-), 47.2 (-N-**C**H_2-CH_2-N-), 50.1 (-N-**C**H_2-CH_2-N-), 51.1 (-N-**C**H_2-CH_2-N-), 51.3(-N-**C**H_2-CH_2-N-), 52.2 (-N-**C**H_2-CH_2-N-), 52.8 (-N-**C**H_2-CH_2-N-), 53.2 ppm (-N-**C**H_2-CH_2-N-)

Attempted synthesis of 4-((1,4,8,11-tetraazacyclotetradecan-1-yl)methyl)benzaldehyde (7)

Cyclam (0.998 mmol, 200 mg) was dissolved in toluene (15 ml) and kept under argon. Sodium hydride (0.998 mmol, 0.025g) was then added and the reaction mixture stirred for 15 minutes. Tris(dimethylamino) borane (1.00 mmol, 190 µl) was then added via syringe. The reaction mixture was refluxed under argon for 5 hours. A solution of **2** (1.20 mmol) in toluene (3 ml) was then added via syringe and the mixture stirred for 1 hour at reflux. The solution was allowed to cool to room temperature before methanol (10 ml) was added. The solvent was removed under vacuum and the crude material redissolved in DCM. Subsequent TLC analysis showed the presence of four spots believed to be multiply substituted products. Purification by silica gel chromatography using the eluent DCM/ MeOH (9:1, volume to volume) yielded **7** in extremely low yield. (31 mg, 10%)

Synthesis of 4-((1,4,8,11-tetraazacyclotetradecan-1-yl)methyl)benzaldehyde (7)

Compound **8** (310 mg, 0.501 mmol) was dissolved in DCM (5 ml). To this solution was added triflouroacetic acid (1 ml). The reaction mixture was stirred for 12 hours at room temperature and becomes yellow over time. Saturated $NaHCO_3$ solution (5 ml) was then slowly added and the mixture stirred for 10 minutes. The mixture was extracted with DCM (2 x 20 ml) and the organic layer dried over $MgSO_4$. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure to yield a yellow oil. IR (ATR) υ = 1692, 1606 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.53 (m, 4H, -CH_2-C**H$_2$**-CH_2-N-), 2.55-2.69 (m, 16H, -N-C**H$_2$**-C**H$_2$**-N-, -C**H$_2$**-N-), 3.59 (s, 2H, N-C**H$_2$**-Ar) 7.40 (d, 2H, $^3J_{H\text{-}H}$ 7.80 Hz Ar-**H**), 7.80 (d, 2H, $^3J_{H\text{-}H}$ 7.99 Hz, Ar-**H**), 9.99 ppm (s, 1H, -C**H**O); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 29.0 (-N-CH_2-**C**H_2-CH_2-N), 29.3 (-N-CH_2-**C**H_2-CH_2-N), 42.0 (-**C**H_2-N-), 42.3(-**C**H_2-N-), 44.0(-**C**H_2-N-

), 44.6(-**C**H_2-N-), 52.3(-**C**H_2-N-), 52.4(-**C**H_2-N-), 129.9 (Ar) 130.1 (Ar), 135.0 (Ar), 145.5 (Ar), 192.0 ppm (-**C**HO)

Synthesis of 1-[4-(Carboxaldehyde)phenylmethyl]-4,8,11-tris-(*tert*-butoxycarbonyl)-1,4,8,11 tetraazacyclotetradecane (8)

A solution of **2** (118 mg, 0.593 mmol) in MeCN (3 ml) was added to a mixture of **3** (200 mg, 0.399 mmol) and K_2CO_3 (81.0 mg 0.586 mmol) in MeCN (10 ml). The mixture was stirred under reflux for 24 hours. After 1 hour the colourless mixture had turned faintly yellow. After 24 hours the yellow mixture was allowed to cool to room temperature and the solid salts were then filtered off. The solvent of the filtrate was removed under reduced pressure. The brown crude material was dissolved in DCM and purified by silica gel chromatography using the solvent mixture DCM/ MeOH (95:5 by volume) as the eluent. This yielded the product as a white powder in 80 % yield (0.293. g). R_f= 0.75 (DCM/MeOH, 10:1); IR (ATR) υ = 1681, 1606 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.43 (s, 27H), 1.69 (m, 2H, -CH_2-C**H$_2$**-CH_2-N-), 1.90 (m, 2H, -CH_2-C**H$_2$**-CH_2-N-), 2.40 (m, 2H,-C**H$_2$**-N-), 2.63 (m, 2H, C**H$_2$**-N), 3.25-3.36 (m, 12H, C**H$_2$**-N-), 3.60 (s, 2H,-N-C**H$_2$**-Ar), 7.43 (d, 2H, $^3J_{H\text{-}H}$ 7.80 Hz, Ar-**H**), 7.80 (d, 2H, $^3J_{H\text{-}H}$ 7.99 Hz, Ar-**H**), 9.98 ppm (s, 1H, C**H**O); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 28.4 (-**C**H_2-CH_2-N-), 28.5 (-C(**C**H_3)$_3$), 46.2 (-**C**H_2-N-) 47.4 (-**C**H_2-N-), 47.6 (-**C**H_2-N-), 51.9 (-**C**H_2-N-), 53.1 (-**C**H_2-N-) 59.6 (-N-**C**H_2-Ar), 79.5 (**C**$(CH_3)_3$), 79.7 (**C**$(CH_3)_3$), 129.7 (Ar), 135.4 (Ar), 146.5 (Ar), 155.5 (-N-**C**OO-), 191.9 ppm (-**C**HO); MS (ESI): *m/z*: 619.45 $[M+H]^+$.

Synthesis of DAB-AM4 with cyclam peripheries (9)

A Schlenk tube was charged with DAB-AM4 PPI (0.040 g, 0.127 mmol) dendrimer and dissolved in 10 ml MeOH. Compound **8** (0.160g, 0.508 mmol) was then added as a solid and the mixture stirred at room temperature under nitrogen for 72 hours. Addition of diethyl ether (20 ml) yielded a yellow precipitate which was filtered and dried to yield **9**. IR(ATR) = 1644 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ_H: 1.44-1.47(br, 27H, -C-(C**H$_3$**)$_3$), 1.68 (m, 8H, -C**H$_2$**-CH_2-N-) 1.83 (m, 8H, -C**H$_2$**-CH_2-N-), 2.52 (m, 16H -C**H$_2$**-N-) 3.26-3.63 (m, -C**H$_2$**-N-, -C**H$_2$**-CH_2-N-), 7.29 (d, 8H, Ar-**H**, , $^3J_{H\text{-}H}$ 7.80 Hz), 7.63 (d, 8H, Ar-**H**, , $^3J_{H\text{-}H}$ 7.98 Hz), 8.26 (s, 4H, -**H**C=N-).

Synthesis of 1,2,4,5-tetrakis(azidomethyl)benzene (10)

A round bottomed flask was charged with 1,2,4,5- tetrakis(bromomethyl)benzene (0.203 g, 0.451 mmol). A solution of sodium azide (0.127 g, 1.956 mmol) in DMSO (4ml) was then added from a freshly prepared 0.5 M stock solution. The reaction mixture was then stirred at room temperature for 24 hours. After 24 hours H_2O (20 ml) was added and the organic product extracted with diethyl ether (3x 20ml). The organic extracts were combined and dried over anhydrous $MgSO_4$. The organic phase was then filtered and the filtrate dried under reduced pressure. Subsequent TLC analysis showed that no further purification was necessary. Yield (97%, 0.129 g) Mp 55-58°C; IR (ATR) υ = 2086, 1570, 1242 cm^{-1}. ^1H NMR ($CDCl_3$) δ_H: 4.47 (s, 8H, -C**H$_2$**-N_3), 7.40 ppm (s, 2H, Ar-**H**). ^{13}C NMR (75 MHz, $CDCl_3$) δ_c: 51.7 (-**C**H_2-N_3), 131.3 (Ar), 134.6 ppm (Ar).

Synthesis of tri-tert-butyl-11-(prop-2-yn-1-yl)-1,4,8,11-tetraazacyclotetradecane-1,4,8-tricarboxylate (11)

To a solution of **3** (0.618 g, 1.24 mmol) in MeCN (30 ml) was added K_2CO_3 (0.256 g, 0.00185 mol). The mixture was then stirred at room temperature for 15 minutes. Propargyl bromide (0.17 ml, 1.6 mmol) was then added via syringe under nitrogen. The mixture was then stirred for 18 hours at reflux under nitrogen. After 18 hours the mixture had turned orange. The mixture was cooled to room temperature and the solid salts were removed by filtration and the filtrate retained. The solvent as well as unreacted propargyl bromide was removed under reduced pressure. The crude material was then dissolved in a mixture of EtOAc and petroleum ether (7:3 by volume) and purified by silica gel chromatography using the same solvent mixture as the eluent. This yielded the product as a white solid in high yield (78%, 0.521 g). Mp 47-49°C; R_f= 0.73 (EtOAc/Pet, 7:3); IR (ATR) υ = 1682, ^1H NMR ($CDCl_3$) δ_H 1.43 (s, 27H, -C(C**H$_3$**)$_3$), 1.65(br, 2H,-CH_2-C**H$_2$**-CH_2-N-), 1.86(br, 2H, -CH_2-C**H$_2$**-CH_2-N-), 2.14 (s, 1H, -C≡C-**H**), 2.47 (t, 2H, $^3J_{H-H}$ 5.27 Hz, -C**H$_2$**-N-CH_2-C≡CH), 2.64 (br, 2H, -C**H$_2$**-N-CH_2-C≡CH), 3.25-3.28 (m, 12H, -C**H$_2$**-N-), 3.36 ppm (s, 2H, -C**H$_2$**-C≡C); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 25.5 (-CH_2-**C**H_2-CH_2-N-), 28.5 (-C-(C**H$_3$**)$_3$), 41.9 (-**C**H_2-CH_2-CH_2-N-), 44.8 (-**C**H_2-CH_2-CH_2-N-), 46.7 (-N-**C**H_2-CH_2-CH_2-N-), 46.9(-N-**C**H_2-

CH_2-CH_2-N-), 47.5(-N-**C**H_2-CH_2-N-CH_2-C≡CH), 48.0(-N-**C**H_2-C≡CH), 50.7(-N-**C**H_2-CH_2-N-), 51.9(-**C**H_2-N-CH_2-C≡CH), 53.0 (-**C**H_2-N-CH_2-C≡CH), 73.2(-C≡**C**H), 77.5 (-**C**≡CH), 79.5 (-**C**(CH_3)), 79.6 (-**C**-(CH_3)$_3$), 155.1 (-**C**OOC-), 155.3 (-**C**OOC-) ; MS (ESI): *m/z* 539 $[M+H]^+$.

Synthesis of 12

To a solution of **11** (0.365 g, 0.680 mmol) in a mixture of THF and H_2O (7 ml/ 3 ml respectively) was added **10** (40.0 mg, 0.134 mmol) and $CuSO_4$·◦$5H_2O$ (10 mol% per azide moiety, 15.0 mg, 0.0570 mmol). The mixture turned faintly blue. Whilst stirring sodium ascorbate (60 mol%, 70.0 mg, 0.353 mmol) was added. Upon the addition of sodium ascorbate the reaction mixture changes colour from blue to yellow-brown. The solution was then stirred at room temperature for 18 hours. After 18 hours ammonia solution (5 ml of a 25 % solution) was added and the mixture stirred for 30 minutes. The reaction mixture was then extracted with chloroform (3 x 20 ml) and the organic phases combined and dried over anhydrous $MgSO_4$, filtered and concentrated under vacuum. Diethyl ether was then added and a precipitate formed. The precipitate was collected by filtration and dried to yield **12** as a cream coloured solid in 78% (0.253 g) yield. IR (ATR) υ = ;^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 1.43 (s, 108H, -C(C**H$_3$**)), 1.69 (br, 8H), 1.86 (br, 8H), 2.41 (br, 8H), 2.59 (br, 8H), 3.33 (m, 40H, -N-C**H$_2$**-C**H$_2$**-N- , -**C**H_2-N-), 3.74 (s, 8H, triazole-C**H$_2$**-Ar), 5.60 (s, 8H, traizole-C**H$_2$**-N-), 7.17 (s, 2H, Ar-**H**), 7.50 (s, 4H, traizole-**H**); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C:

Attempted synthesis 13

Compound **12** (0.253 g, 0.105 mmol) was dissolved in 10 ml DCM. To this solution was added triflouroacetic acid (2.5 ml). The reaction mixture was stirred for 24 hours at room temperature. Saturated $NaHCO_3$ (10 ml) solution was then slowly added and the mixture stirred for 20 minutes. The mixture was extracted with DCM (3 x 20 ml) and the organic layer dried over $MgSO_4$. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. Subsequent analysis by FT-IR and ^{1}H NMR spectroscopy confirmed the presence of Boc.

Synthesis of 1,4,8,11-tetrakis(2-methoxycarbonylethyl)-1,4,8,11-tetraazacyclotetradecane (14)

Cyclam (0.200 g, 0.998 mmol) was dissolved in MeOH (3 ml). A solution of methyl acrylate (11 ml, 0.12 mol) in MeOH (5 ml) was then added via syringe. The mixture was stirred at room temperature under a nitrogen atmosphere for 48 hours. After 48 hours the solvent and unreacted methyl acrylate was removed under reduced pressure to yield a colourless oil. The crude material was dissolved in a small amount of DCM and purified by silica gel chromatography using the eluent DCM/MeOH, 9:1 (by volume). This gave the product as a viscous colourless oil in high yield (490 mg, 90%). R_f= 0.65 (DCM/MeOH, 9:1); IR (ATR) υ = 1728.9 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ_H 1.56 (q, 4H, $^3J_{H-H}$ 6.75 Hz, -CH_2-C**H$_2$**-CH_2-N-) 2.40-2.50 (m, 24H, -C**H$_2$**-N), 2.74 (t, 8H, $^3J_{H-H}$ 7.04 Hz, -N-C**H$_2$**-CH_2COO-), 3.67 ppm (s, 12H, -COO-C**H$_3$**) ^{13}C NMR (75 MHz, $CDCl_3$) 24.0 (-**C**H_2-CH_2-N-), 32.4 (-**C**H_2-COO-), 50.5 (-COO-**C**H_3), 51.2 (-N-**C**H_2-CH_2-COO-), 51.3(-N-**C**H_2-CH_2-**C**H_2-N-), 51.5(-N-**C**H2-**C**H2-N-), 173.2 ppm (-**C**OO-); MS (ESI): *m/z* 546 $[M+H]^+$.

Synthesis of 1,4,8,11-tetrakis(2-(N-(2-aminoethyl)carbamoyl)-ethyl)-1,4,8,11-tetraazacyclotetradecane (15)

14 (0.490 g, 0.900 mmol) was dissolved in MeOH (5 ml). To this solution ethylene diamine (7.2 ml, 107.9 mmol) was added via syringe. The reaction was stirred under argon atmosphere for 3 days in the dark. After 3 days excess ethylene diamine and the solvent, MeOH, were removed under reduced pressure. The crude material obtained was then stirred in diethyl ether. After 1 hour a cream coloured precipitate started forming. After stirring in diethyl ether for another hour, stirring was stopped and the supernatant was removed with a syringe. This process of stirring the compound in diethyl ether followed by the removal of the supernatant was repeated a total of four times. This yielded compound **15** as a yellow powder in high yield (80%). IR (ATR) υ = 3293, 1628 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ_H 1.50 (br, 4H, -N-CH_2-C**H$_2$**-CH_2-N-), 2.17 (t, 8H, $^3J_{H-H}$ 6.75 Hz, -N-C**H$_2$**-C**H$_2$**-N-), 2.39-2.43 (m, 16H, -C**H$_2$**-N-, C**H$_2$**-CONH-), 2.54-2.59 (m, 12H, -N-C**H$_2$**-CH_2-CONH-), 2.90 (br, 8H, -C**H$_2$**-NH_2) 3.01 (q, 8H, -CONHC**H$_2$**-) 7.93 ppm (t, 4H, $^3J_{H-H}$ 5.14 Hz, -CON**H**CH_2-); ^{13}C

NMR (100 MHz, DMSO-d_6), 23.4 (-N-CH_2-**C**H_2-CH_2-N), 33.2 (-**C**H_2-COO-), 41.0 (-**C**H_2-NH_2), 41.4 (-CONH-**C**H_2-CH_2-NH_2), 50.1 (-N-**C**H2-**C**H2-N-),), 50.5 (-N-**C**H_2-CH_2-COO-), 50.8 (-N-**C**H_2-CH_2-**C**H_2-N-), 171.6 ppm (-**C**ONH-); MS (ESI) *m/z*: 658 $[M+H]^+$

Synthesis of 3,3',3'',3'''-(1,4,8,11-tetraazacyclotetradecane-1,4,8,11-tetrayl)tetrakis(N-(2-hydroxybenzylidene)amino)ethyl)propanamide) (16)

Compound **15** (200 mg, 0.300 mmol) was dissolved in MeOH (10 ml). Salicylaldehyde (0.147 g, 1.20 mmol) was added via syringe. The mixture turned yellow immediately. The mixture was stirred at room temperature under argon for 48 hours. A yellow precipitate formed. After stirring for 48 hours the mixture was cooled to 0°C and kept at 0°C for an hour. The precipitate collected by filtration and washed with cold MeOH (2 x 20 ml) and diethyl ether (1 x 20 ml). The compound obtained was dried under vaccum to afford the pure dendrimer as a yellow powder in moderate yield (0.23 g, 71%). Mp 167-169°C; IR (ATR) υ = 3296,1629, 1579 cm^{-1}, ^{1}H NMR (600 MHz, CD_3Cl) δ_H : 1.35 (br, 4H, -C**H$_2$**-CH_2-N-) 2.24-2.25 (-CH_2-C**H$_2$**-N-) 2.35 (s, 8H, -C**H$_2$**-N-), 2.53 (t, 8H, $^3J_{H-H}$ 5.86 Hz, -C**H$_2$**-CONH-), 3.52 (q, 8H, $^3J_{H-H}$ 5.57 Hz, -CO-NH-C**H$_2$**-) 3.70 (t, 8H, $^3J_{H-H}$ 5.27 Hz, -C**H$_2$**-N=C-), 6.85-6.90 (m, 8H, **H**-Ar), 7.20 (d, 4H, Ar-**H**), 7.28 (t, 4H, Ar-**H**), 7.80 (br, 4H, Ar-**H**), 8.30 (s, 4H, -C**H$_2$**=N-), 13.24 ppm (br, 4H, Ar-O**H**); ^{13}C NMR (600 MHz, CD_3Cl) δ_c : 22.4 (-N-CH_2-**C**H_2-CH_2-N-,), 33.0 (-N-CH_2-**C**H_2-CONH-CH_2-), 39.9 (-CH_2CONH-**C**H_2-), 49.17 (-N-**C**H_2-**C**H_2-N-), 50.5 (-N-**C**H_2-CH_2-**C**H_2-N-), 51.0 (-N-**C**H_2-CH_2-CONH-), 58.6 (-**C**H_2-C=N), 116.9 (Ar), 118.6 (Ar), 118.8 (Ar), 131.4 (Ar), 132.5 (Ar), 161.0 (-**C**=N-), 166.4 (Ar-OH), 172.7 ppm (-NH**C**O-); MS (ESI) *m/z*: 1073 $[M+H]^+$.

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CHAPTER 3: SYNTHESIS OF METALLODENDRIMERS AND THEIR APPLICATION IN THE CATALYTIC OXIDATION OF BENZYL ALCOHOL

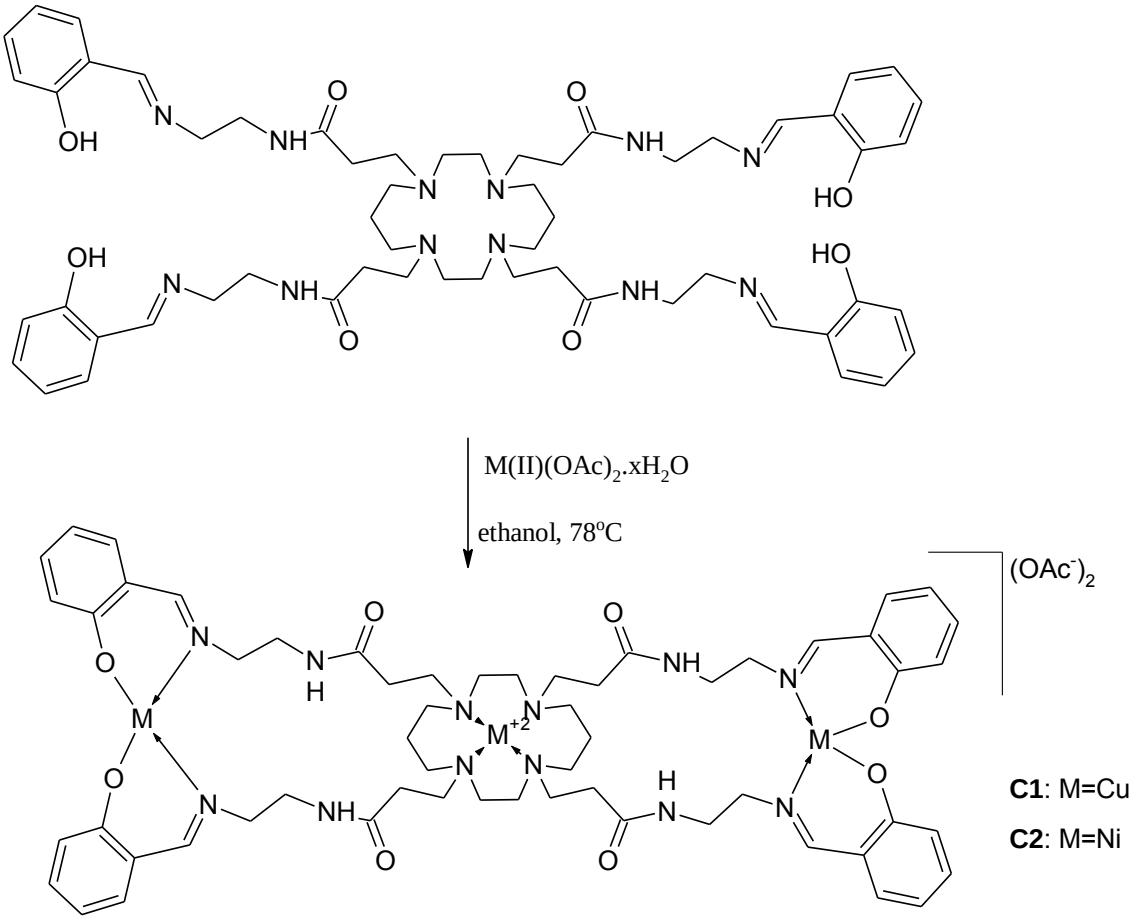
3.1 Introduction to metallodendrimers

The incorporation of transition metal ions into dendrimer scaffolds, with their often unusual and unique properties have received widespread attention in the last 15 years or so and have been the subject of several reviews.[1-3] These metallodendrimers find application amongst others in the fields of catalysis and the biomedical sciences.[4,5] Metallodendrimers often exhibit unique properties that are not present in the non metallated dendrimer nor in the metal bearing subunit.[6] These properties can give rise to so called positive and negative dendritic effects. These dendritic effects can influence, for example, the catalytic activity, selectivity, stability, and solubility of these metallodendrimers when compared to the non metallodendrimer analogues. Metallodendrimers and metallopolymers are attractive candidates for use as reusable catalysts due to their high molecular masses and therefore ease of separation either by precipitation or ultrafiltration and ultracentrifugation.[6]

3.2 Synthesis and characterization of metallodendrimers based on ligand **16**

A range of different metallodendrimers was synthesized by the reaction of the appropriate transition metal salt with the dendritic ligand **16**, reported in Chapter 2. This reaction is outlined in Scheme 3.1. The synthesis was performed by following a modified literature procedure for the preparation of dendritic salicylaldimine

complexes.[7] By varying the nature of the metal acetate used, a range of metallodendrimers was synthesized that included Cu(II), Ni(II) and Zn(II) analogues. A similar metal complex was reported by Mahdavi *et al* who prepared a Pd(II) complex of poly[N-(2-aminoethyl)acrylimido]-imino-salicylaldehyde.[8]



Scheme 3.1: General synthetic method employed for the synthesis of C1 and C2

3.2.1 Synthesis and characterization of Cu(II) metallodendrimer, **C1**

The synthesis was performed by modifying a literature procedure to use copper acetate as metal precursor. The material obtained was characterized by FT-IR, UV-Vis spectroscopy, mass spectrometry, magnetic susceptibility, thermogravimetric analysis and electron paramagnetic resonance spectroscopy.

FT-IR spectroscopy

The FT-IR spectrum of complex, **C1** showed a shift in the imine signal from 1627 cm^{-1} in the ligand to 1617 cm^{-1} in the complex. This is an indication of coordination of the imine to the Cu(II) center. The broad resonance associated with the O-H stretch present in the ligand spectrum, is no longer observed. Furthermore a broad peak ranging from 1610-1538 cm^{-1} is observed. This broad peak might be due to overlapping of the aromatic signals observed at 1573 cm^{-1} and the signal due to the acetate carboxylate which is usually observed around 1597 cm^{-1}. The C-O stretch of the acetate counter ion is observed just above 1400 cm^{-1}. Similar results for analogous complexes are reported in the literature.[9]

UV-Vis spectroscopy

The UV-Vis spectra of both the ligand **16** and the Cu(II) metallodendrimers **C1** are shown in Figures 3.1-3.2.

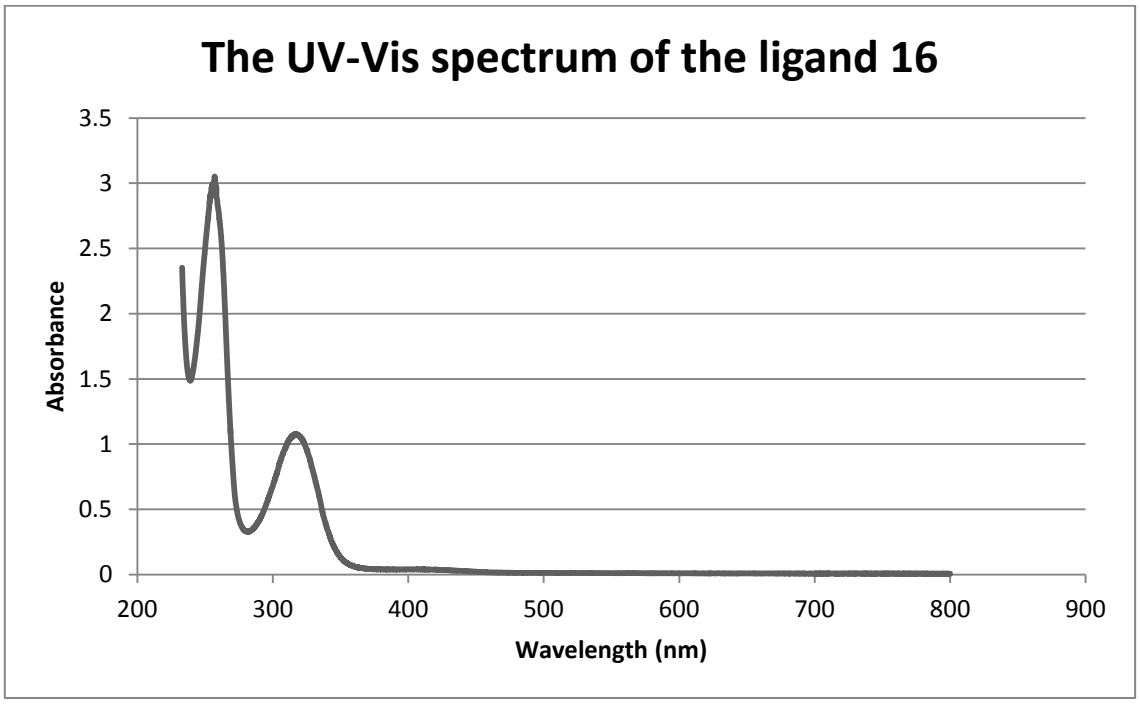


Figure 3.1: The UV-Vis spectrum of the dendritic ligand 16

The UV-Vis spectrum of **C1** shows a total of 5 absorption bands. The bands at 225 (not fully resolved in Figure 3.1 due to solvent cutoff) and 260 nm (Figure 3.2) are present in the ligand spectrum as well (Figure 3.1). These are assigned to π- π* transitions of the ligand. An additional absorption band is seen ranging from 300 to

400 nm (325 nm in the ligand spectrum and around 360 nm in the spectrum of **C1**). A shoulder is visible in this range. This is most likely due to overlapping of several of the metal to ligand charge transfer bands. This can be ascribed to the two different chemical environments of the Cu(II) centers namely those on the periphery and that at the core of the dendrimer .

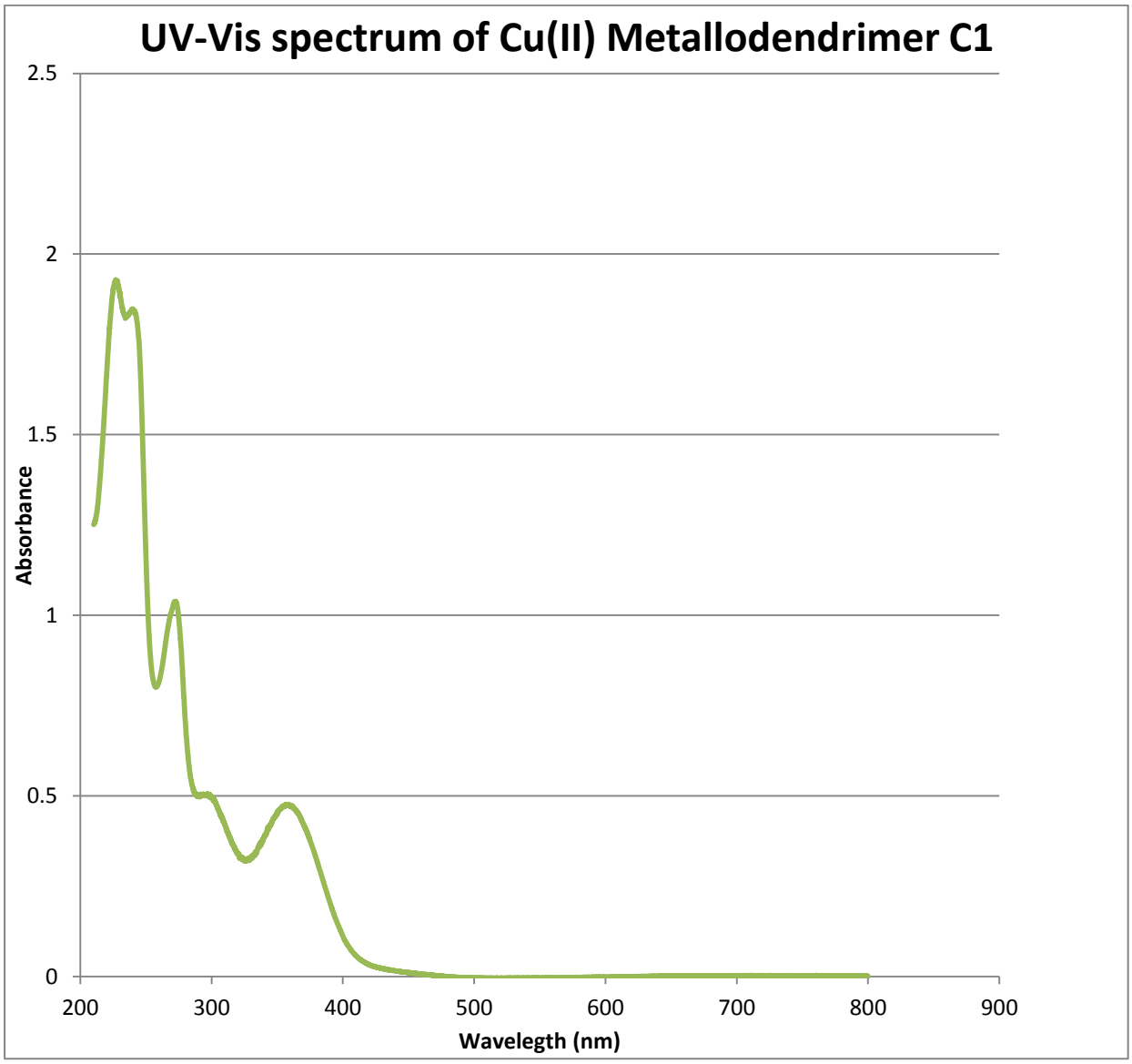


Figure 3.2: UV-Vis Spectrum of C1

Mass spectrometry

A mass spectrum (ESI, positive mode) of **C1** showed an isotopic cluster centered at *m/z* 1259 which conforms to the expected molecular ion of the complex. This

correlates to the mass of the ligand and three Cu(II) centres.[10, 11] The high *m/z* range fragmentation pattern can be understood as the sequential loss of copper ions from the molecule starting at *m/z* 1258.4 $(M)^+$, 1197.5(M-Cu+H) and 1134.5(M-2Cu). The base peak is observed at *m/z* 629.7 which is assigned as the *m/2* peak; the doubly charged molecular ion.

Magnetic susceptibility measurements

A magnetic susceptibility measurement was performed on the material. A value of 3.01 BM was obtained, indicating that the material is paramagnetic. This value is higher than that expected for a single isolated Cu^{2+} center.

EPR spectroscopy

An attempt at characterizing the complex using electron paramagnetic resonance (EPR) spectroscopy was not entirely successful as the EPR spectrum obtained consisted of broad lines that do not show hyperfine coupling of the unpaired electron of the metal centre with the nitrogen donors of the ligand. This behaviour has previously been observed by others for the EPR spectra of multinuclear Cu(II) complexes.[12, 13] The broad signal and lack of hyperfine coupling is most likely due to a weak interaction between the different Cu(II) centers of the molecule.[13]

TGA analysis

Thermogravimetric analysis was performed to investigate the thermal stability of the dendritic scaffold and the metallodendrimer. The figures below show the TGA spectra of firstly, the ligand (Figure 3.3) and then the Cu metallodendrimer (Figure 3.4).

The TGA plot of the dendritic ligand (Figure 3.3) shows a very small mass loss below 100°C which can be attributed to the loss of encapsulated solvent molecules. Furthermore the thermal plot shows that the organic dendritic scaffold is thermally stable up to around 200°C at which temperature a large mass loss is observed. From this point onward the derivative graph never reaches zero again, indicating continuous mass loss after 200°C. This is probably related to the total decomposition of the material.

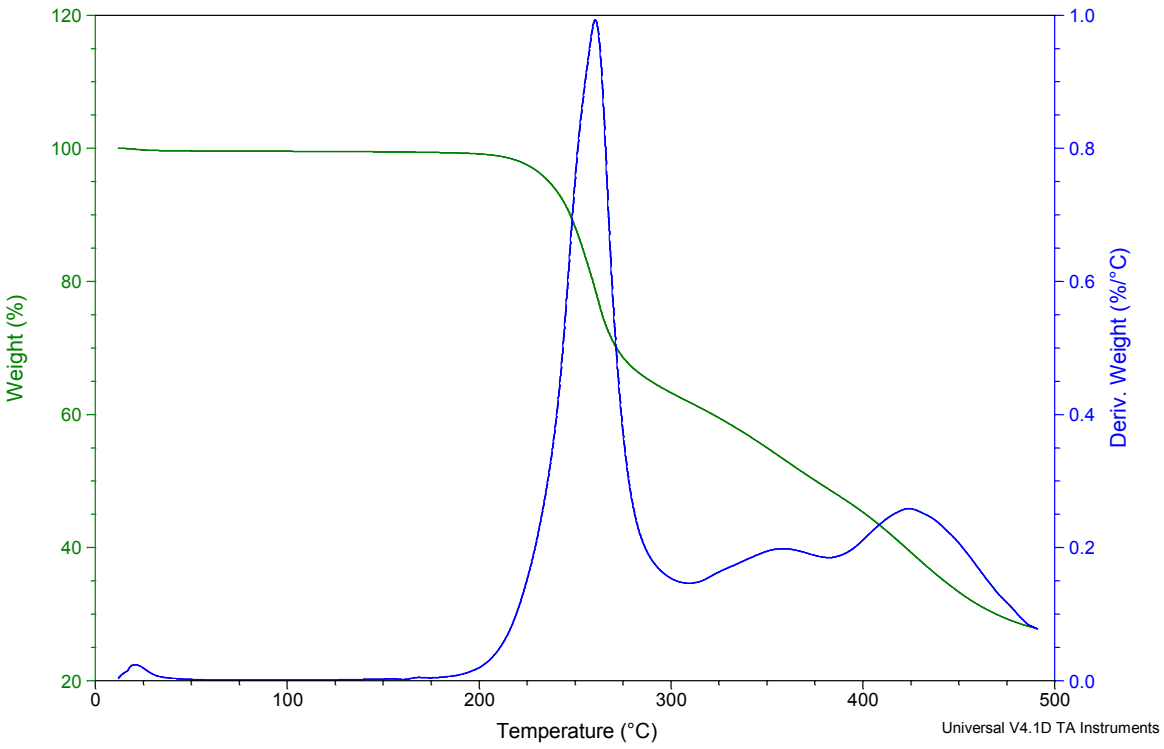


Figure 3.3: TGA of ligand 16

The TGA plot of complex **C1** (Figure 3.4) shows 4 thermal events. The first mass loss is due to the loss of entrapped solvent molecules from the product. By comparing the ligand TGA plot with that of the metallodendrimer it is observed that the first derivative plot of the metallodendrimer has an extra mass loss peak (local maximum at 175°C). This mass loss corresponds to 7.3 % of the total mass. This is most probably due to the loss of the acetate counter ion (8% of total mass of the proposed structure). A very large mass loss then occurs starting between 200 and 225°C. This likely indicates that decomposition of the dendritic ligand starts to take place as the dendritic ligand accounts for the majority of the mass. It appears that the dendritic ligand decomposition takes place in two stages. At the temperature range of 200-300°C about 30% of the remaining mass decomposes. A further 15% of the total mass decomposes in the range 300-500°C resulting in the metal oxide at high temperatures (500°C).

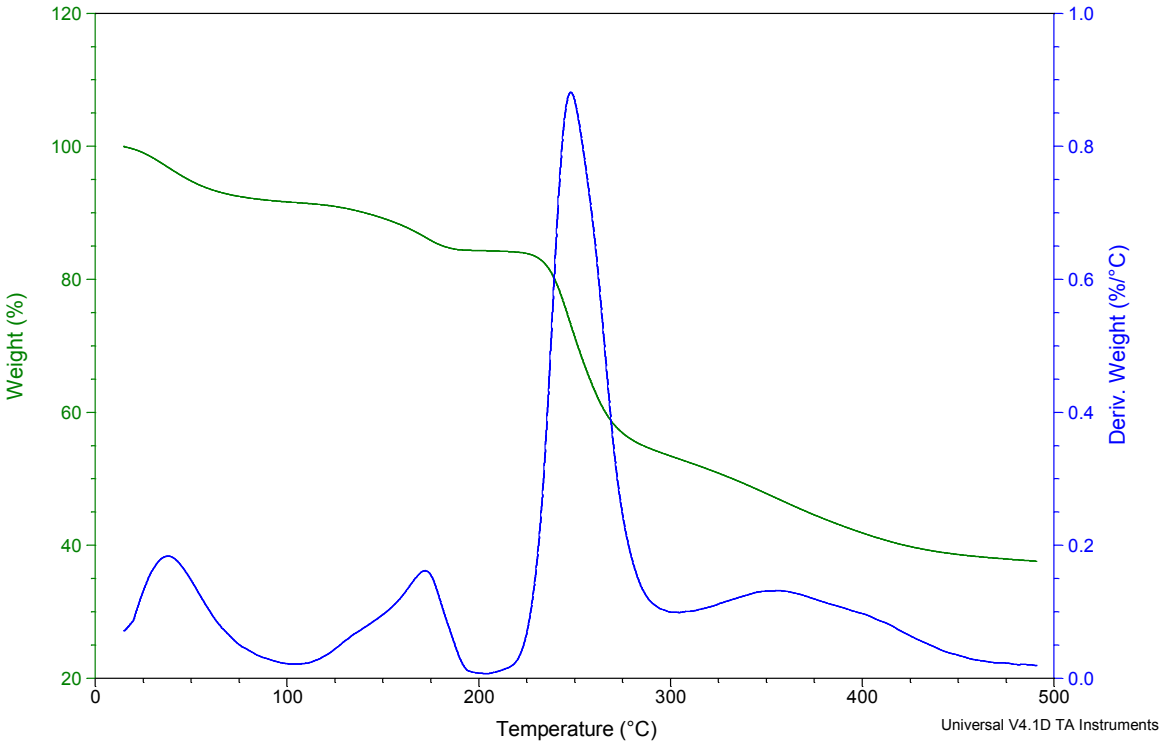


Figure 3.4: TGA of C1

Elemental analysis

Further characterization of **C1** by elemental analysis indicates the inclusion of water molecules within the dendrimer architecture. This, however, is not unusual for metallodendrimers with polyamino scaffolds.

3.2.2 Synthesis and characterization of Ni(II) metallodendrimer **C2**

The Ni(II) metallodendrimer was synthesised in an analogous manner to that employed for the Cu(II) metallodendrimer by using nickel acetate tetrahydrate as the metal precursor.[7] The product precipitated out of solution to yield a green-brown solid. The material obtained was characterized by a range of techniques (FT-IR, UV-Vis spectroscopy, ESI-MS, TGA and magnetic susceptibility measurements).

FT-IR spectroscopy

The FT-IR spectrum showed a shift of the imine signal from 1629 to 1612 cm^{-1}. This indicates coordination between the imine and the metal center. One broad peak is observed in the range 1600-1539 cm^{-1}. The broadness likely occurs because of overlapping peaks. The acetate carboxylate usually has a signal around 1597 cm^{-1}, furthermore aromatic $\upsilon_{C=C}$ bands are also normally observed in this range as well.

UV-Vis spectroscopy

The UV-Vis spectrum (Figure 3.5) showed peaks at 225 and 240 nm. An unresolved shoulder is also observed at 266 nm. The ligand (Figure 3.1) shows similar absorption peaks. These are therefore likely π- π* transitions of the ligand. A further absorption maximum is observed at 367 nm which is likely a metal to ligand charge transfer band. An unresolved shoulder is also observed around 400 nm. This is likely due to forbidden d-d transitions of the Ni(II) centers. Simmilar results are reported by other authors for Ni(II) salicylaldimine complexes.[14]

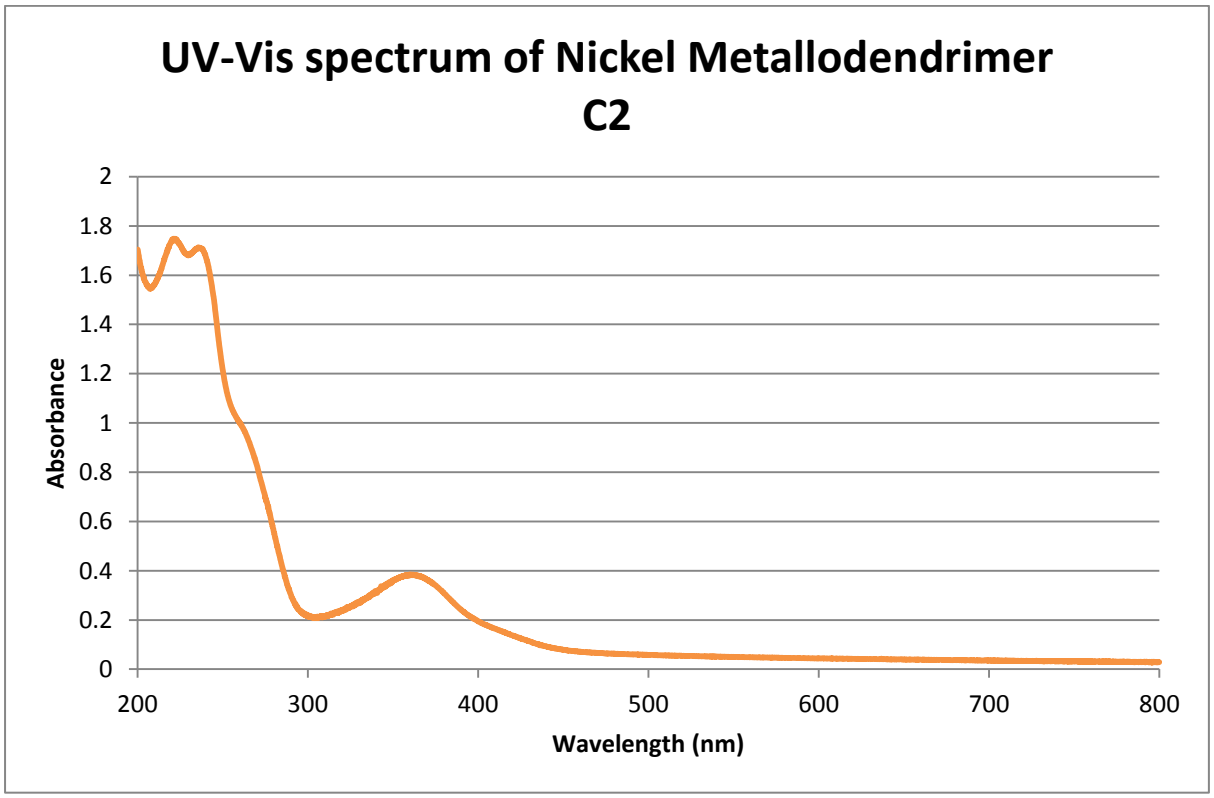


Figure 3.5: UV-Vis spectrum of C2

Mass spectrometry

The ESI-MS spectrum showed a cluster centred at *m/z* 1245 which is due to the molecular ion of the tri-nuclear complex. The sequential loss of metal ions observed in the mass spectrum of **C1** is not observed in the case of the nickel metallodendrimers **C2**. Besides the molecular ion at m/z 1245, the only other significant peaks are those associated with the ligand i.e. peaks associated with fragments in which all the metals are lost.

Magnetic susceptibility measurements

The magnetic moment of the nickel metallodendrimer was measured and a value of 4.1 BM was obtained. This is slightly higher than that usually expected for isolated Ni(II) systems. This could be due to antiferromagnetic interactions between the three Ni(II) centers.[13]

EPR spectroscopy

A suitable EPR spectrum of the dendrimer could not be obtained under the conditions employed. A spectrum was recorded at room temperature and in the solid state. Unfortunately no resonance peaks were observed in the EPR spectrum. Other authors have reported similar results for the EPR spectroscopy of similar Ni(II) species under these conditions.[15] The nickel(II) ion (d^8) is a non-Kramer ion, an ion with unpaired electrons but with an even number of electrons overall. These ions usually only show EPR resonances at liquid helium temperatures.[15] Even at such low temperatures the resonances are often broad and lack hyperfine splitting. In some cases no resonance is observed for non-Kramer ions, even at low temperatures. This can be due to the quantum of energy necessary for a spin change being outside the frequency range of the microwave used in the EPR experiment.

TGA analysis

The TGA of **C2** is shown in Figure 3.6. As was observed for the copper complex **C1**, a mass loss below 100°C is observed, likely due to encapsulated solvent (local maximum below 100°C). A second mass loss is then observed in the temperature range between 100 and 250°C. This mass loss is not observed during the

decomposition of the pure ligand, it is however observed for **C1**. Likely nickel oxide remains at high temperatures.

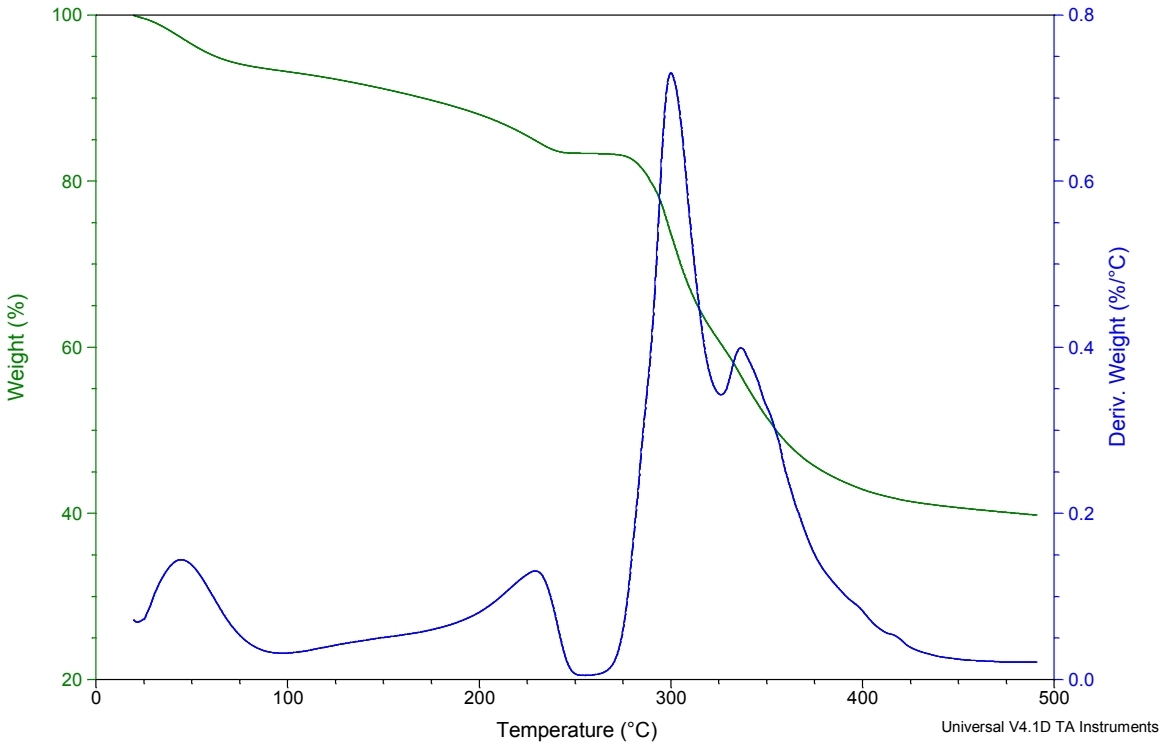


Figure 3.6: TGA of C2

Elemental analysis

Further characterization was attempted using elemental analysis. Elemental analysis seem to indicate the encapsulation of a number of water molecules into the dendrimer matrix. Such a phenomenon is not rare for metallodendrimers with polyamino scaffolds.

3.2.3 Synthesis and characterization of Zn(II) metallodendrimer **C3**

The synthesis of **C3** was carried out by modifying the procedure used for **C1** and **C2**. Zinc acetate was used as metal salt. Purification of the compound was performed in an analogous manner to **C1** by first precipitating any unreacted ligand followed by precipitation of the complex using diethyl ether.

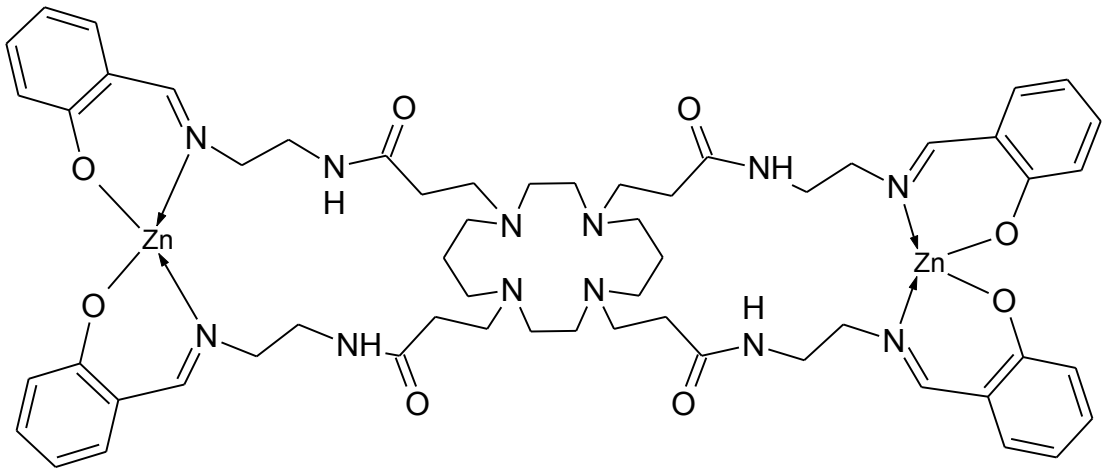
C3 was characterized by FT-IR, ^{1}H NMR, ^{13}C NMR, and ESI-MS. Similar to what was observed in the FT-IR spectra of **C1** and **C2**, the O-H stretch observed in the ligand spectra is no longer present in the complex, **C3**, spectrum. Additionally, the C=N stretch is shifted to lower wavenumber (1617 cm^{-1}) indicating successful coordination.

The ^{1}H NMR spectrum, no longer showed the resonance at 13.24 ppm assigned as the C-O**H** resonance. In addition the imine proton resonance is shifted downfield in the product spectrum (to 8.42 ppm in DMSO-d_6, broad) which indicates successful coordination to the Zn^{2+} ion.

Similarly in the ^{13}C NMR spectrum of **C3** the imine carbon as well as the phenolic carbon (Ar-OH, in the ligand, Ar-O^- in complex) are shifted downfield to 175.2 and 170.3 ppm, respectively, due to the deshielding effect of the coordination of the Zn^{2+} ion to the salicylaldimine units. However no shifts are observed for the cyclam carbons (-**C**H_2-N-, -**C**H_2CH_2-N-) which seem to indicate that coordination probably does not take place through the cyclam amines. This could be due to the lower stability of the cyclam moiety with Zn(II) compared to Cu(II) and Ni(II). Such lower stability of zinc-cyclam complexes has previously been observed.[16]

The mass spectrum of **C3** does not show the molecular ion, instead extensive fragmentation is evident under the conditions employed. Amongst the signals observed is a signal at *m/z* 1136 which can be assigned as the ligand and one Zn metal center $[M + H^+ - Zn]^+$. A further signal at *m/z* 1073 is observed which is assigned as the molecular ion of the ligand.

In light of the characterization data compound **C3** likely only has two coordinated Zn(II) metal centers as shown in Figure 3.7.



C3

Figure 3.7: The proposed structure of C3

3.3 Catalytic oxidation of alcohols

The oxidation of primary and secondary alcohols to carbonyl compounds such as aldehydes, ketones and carboxylic acids is one of the most commonly performed organic transformations and has been the subject of many reviews. [17, 18] Numerous oxidizing agents have been reported to be active for this transformation such as potassium permanganate and Jones' reagent (chromium trioxide in dilute sulphuric acid).[19, 20] The use of many of these reagents are however undesirable due to the use of stoichiometric amounts which can be costly. Furthermore these reagents are often toxic for example the Cr^{4+} and Cr^{6+} reagents are known carcinogens.

The above mentioned disadvantages have motivated researchers to look for oxidative methods with better atom economy (preferably catalytic methods) that use environmentally friendly oxidants such as H_2O_2, molecular O_2, or even air. Oxidation processes using a catalytic amount of transition metal complexes such as those of Mn^{2+}, Cu^{2+}, Pd^{2+} and Ru^{2+} have been reported. [21-24]

Berkessel *et al* reported a catalytic oxidation system that consisted of the macrocycle, 1,4,7-trimethyl-1,4,7-triazacyclononane, and manganese(II) acetate in the presence of H_2O_2. This system showed high catalytic activity for the oxidation of pentan-2-ol to pentan-2-one.[25]

Copper is often used in catalytic oxidation reactions along with nitroxyl radicals. These systems were first reported by Brackman and Gaasbreek who used a copper phenanthroline complex along with a di-tert-butylnitroxyl radical for the oxidation of methanol to formaldehyde.[26] Semmelhack *et al* then reported a catalytic alcohol oxidation system composed of CuCl along with the nitroxyl radical, 2,2,6,6-tetramethylpiperidinyl-1-oxyl (TEMPO) for the oxidation of alcohols.[27]

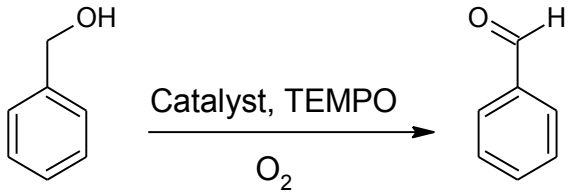
Recently copper salen transition metal complexes along with the co-catalyst TEMPO were tested for the catalytic alcohol oxidation of benzylic, allylic and aliphatic alcohols.[22] This catalyst was tested in the oxidation of benzyl alcohol to benzaldehyde. The catalytic system was able to furnish the product, benzaldehyde in quantitative yield after 10 hours using toluene as solvent and heating the mixture at 100°C using molecular oxygen at atmospheric pressure.

Ahmad *et al* reported a new catalytic system utilising a range of copper (II) salicylaldimine transition metal complexes along with TEMPO as co-catalyst.[28] The catalysts showed high activity in the oxidation of benzylic and allylic alcohols to the corresponding aldehydes even when operating under fairly mild conditions such as low catalyst loading (0.66 mol%) and 1 atmosphere of O_2 pressure and temperatures between 60°C and 100°C.

In summary there exists a need for processes that oxidize alcohols to carbonyl compounds with the following desirable characteristics.

- System should be catalytic (preferably recyclable)
- Operate under mild conditions
- Use environmentally friendly oxidants

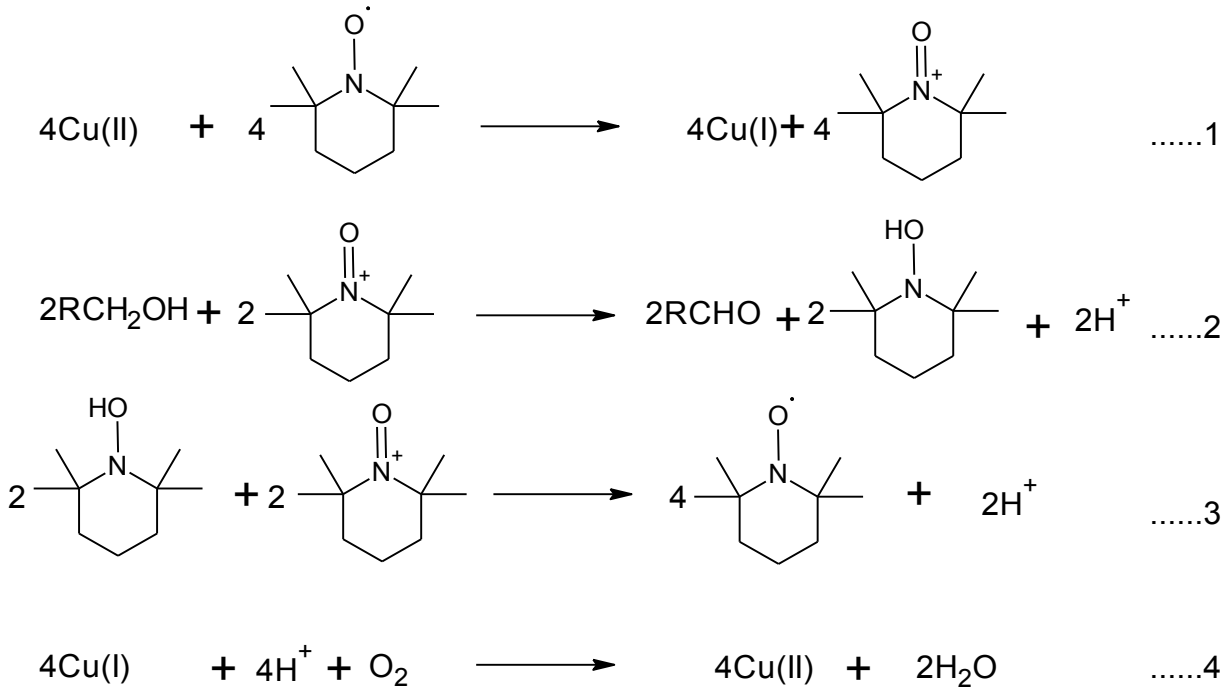
To this end some of the synthesised metallodendrimers were tested as catalysts for the oxidation of alcohols to aldehydes using molecular oxygen as oxidant. The oxidation of benzyl alcohol was chosen as a model reaction to test the effectiveness of the catalysts. As shown in Scheme 2, the catalytic system is composed of the catalyst, TEMPO and O_2.



Scheme 3.2: Model oxidation reaction of benzyl alcohol to benzaldehyde

3.3.1 The proposed catalytic cycle

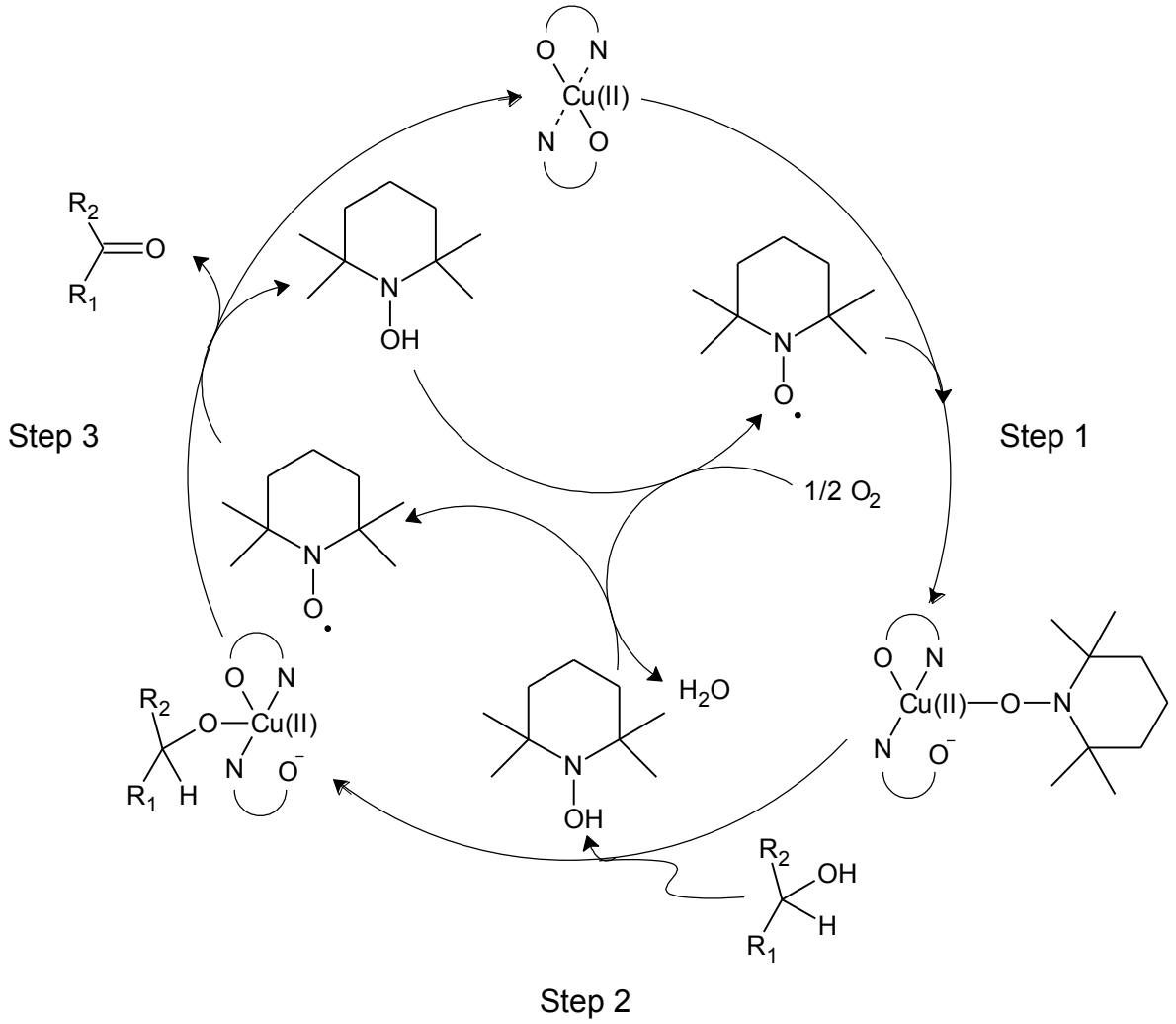
As previously mentioned, catalytic systems consisting of copper catalysts along with TEMPO have been previously reported. The exact nature of the mechanism for this reaction however is still not entirely certain. Semmelhack *et al* initially proposed a mechanism whereby the copper complex oxidizes TEMPO to the oxoammonium cation (Scheme 3.3 reaction 1) which acts as the actual oxidant (Scheme 3.3 reaction 2). [29] The oxoammonium cation oxidizes the alcohol to the corresponding aldehyde while also forming TEMPOH. The TEMPOH undergoes syn proportionation with the oxoammonium cation to regenerate TEMPO (Scheme 3.3 reaction 3). Finally the Cu(I) is oxidized back to Cu(II) using O_2.



Scheme 3.3: Proposed mechanism by Semmelhack[27]

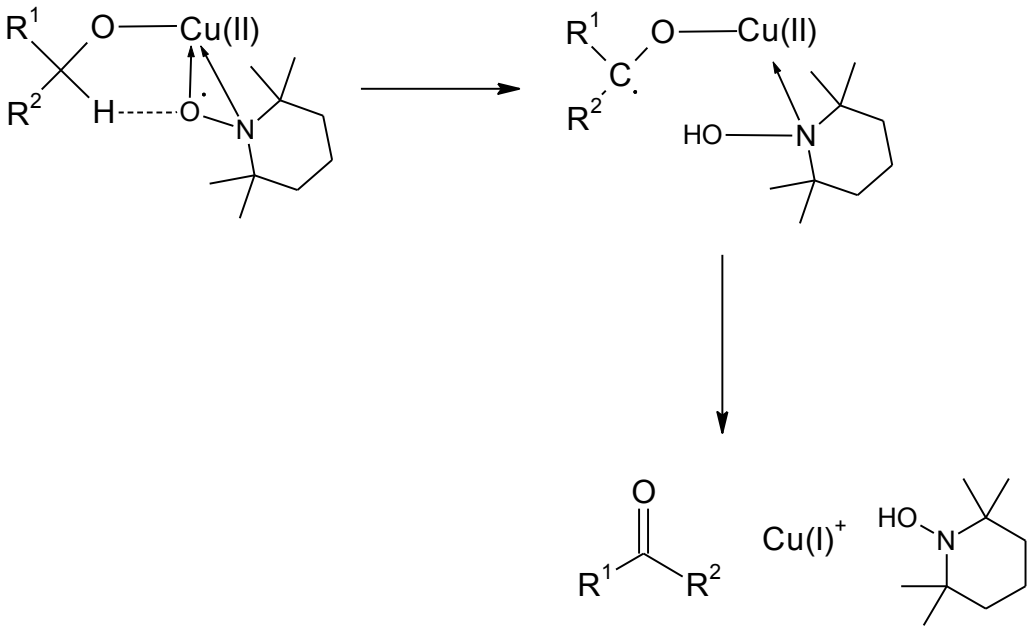
Several Years later Sheldon *et a*l reinvestigated the mechanism by drawing inspiration from the related Ru/TEMPO system.[30] These workers argued that the Cu/TEMPO system's mechanism likely did not involve the oxoammonium ion. By testing the catalytic system on both benzylic and aliphatic alcohol substrates it was found that aliphatic alcohols were not converted to their corresponding aldehydes. This result did not seem to be consistent with oxoammonium oxidations which are known to have broad scope, oxidizing simple aliphatic alcohols as well as benzylic alcohols.[31] It was then shown experimentally that Cu(I) is oxidized by TEMPO under an inert atmosphere. In a subsequent experiment CuCl, TEMPO and benzyl alcohol was added to the reaction mixture (under an inert atmosphere). The reaction produced a small amount of benzaldehyde. In light of these experimental results Sheldon *et al* proposed the alternative mechanism shown in Scheme 3.4.

During the catalytic cycle (Scheme 3.4, Step 1) TEMPO coordinates to the Cu(II) center. Intramolecular hydrogen transfer takes place followed by oxidative elimination to yield the product carbonyl (Step 3). This is in contrast to the Semmelhack mechanism which identified an oxoammonium cation as the active catalyst. The catalytic cycle also shows that TEMPO-H is formed and is oxidized back to TEMPO with half a mole equivalent of O_2 while TEMPO in turn oxidizes Cu(I) back to Cu(II).



Scheme 3.4: The catalytic cycle proposed by Sheldon *et al*[28]

Scheme 3.5 is a more detailed expansion of the processes that occur during steps 2 and 3 of the catalytic cycle shown in Scheme 3.4 and shows the formation of an alkoxycopper(II)/TEMPO complex with TEMPO coordinated to the Cu(II) center in an η^2 fashion. The subsequent intramolecular hydrogen abstraction as well as the formation of Cu(I), the product carbonyl and TEMPOH are also shown.



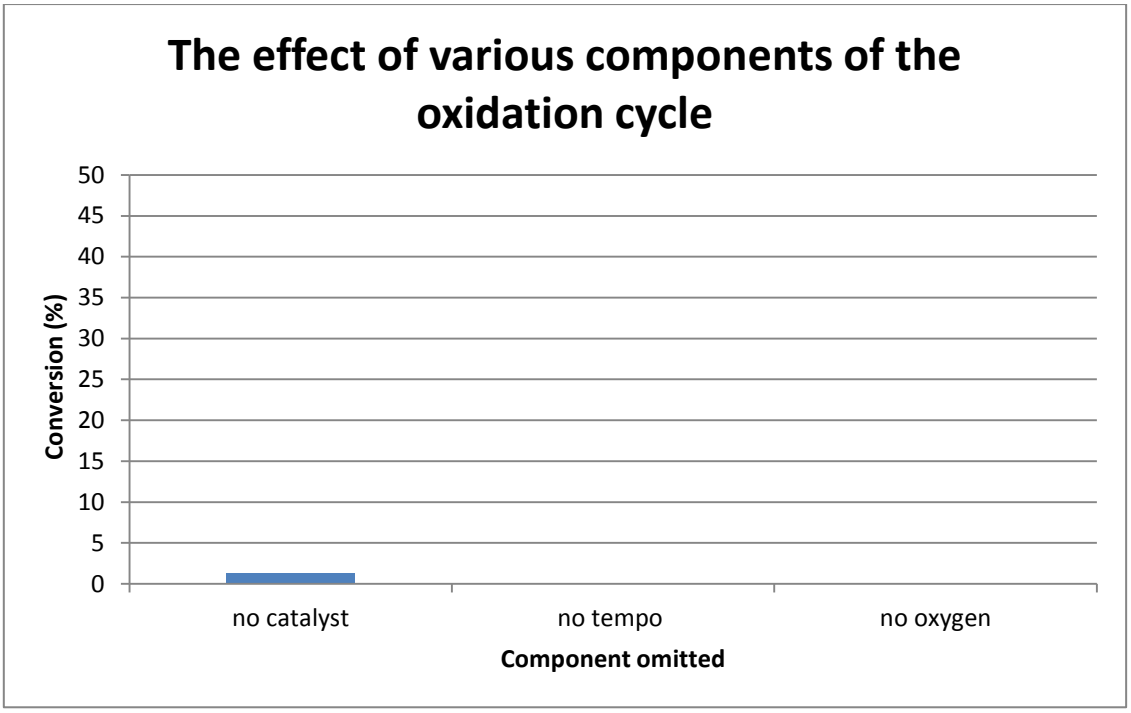
Scheme 3.5: Intramolecular hydrogen transfer and subsequent oxidative elimination

3.3.2 The application of **C1** and **C2** in the oxidation of alcohols

The complexes **C1** and **C2** were tested as catalysts for the oxidation of benzyl alcohol to benzaldehyde. First the influence of the various components (catalyst, co-catalyst and oxygen) described in Semmelhack and Sheldon's mechanisms were tested. The influence of the reaction paramaters namely, the nature of the solvent, catalyst concentration, substrate concentration, temperature and time were evaluated in order to optimize the reaction.

3.3.2.1 The effect of the different components of the catalytic system

The influence of each of the proposed components (catalyst, TEMPO, substrate and O_2) of the catalytic system was tested by sequentially omitting one component and testing the system in the proposed catalytic reaction. The results of these experiments are shown in Figure 3.8.



Reaction conditions: 3h, 0.96 mmol benzyl alcohol, 100°C 1.3 mol% TEMPO, 0.33 mol% Cu, 1 atm O_2, DMF as solvent 2.02 ml total volume.

Figure 3.8: The effects of different components on the catalytic cycle

The reaction was first performed without the metallodendrimer catalysts. The reaction mixture therefore consisted of benzylalcohol (the substrate), DMF (solvent) and TEMPO. The reaction was heated to 100°C and 1 atmosphere of O_2 pressure was applied to the reaction vessel. It was observed that without catalyst only a small degree of oxidation does take place. This is attributed to TEMPO acting as a weak oxidant on its own.

An experiment was then performed where TEMPO was omitted from the reaction mixture. After stirring at a temperature of 100°C for 3 hours the sample was analysed. No conversion of benzyl alcohol to benzaldehyde was observed in the absence of TEMPO. In the proposed catalytic cycle (Scheme 3.4) Cu(I) is oxidized to Cu(II) to complete the cycle. Without TEMPO this redox cycle cannot occur. This is likely the reason that no conversion was observed for this test reaction. TEMPO is therefore essential for the reaction to take place.

The next test reaction was performed in the absence of O_2. The reaction was performed under an argon atmosphere. After 3 hours the reaction was stopped and

the reaction mixture analysed. No product formation was observed. It is therefore essential to the catalytic system that some form of primary oxidant is present. According to the catalytic cycle, oxidation of the alcohol to the corresponding carbonyl also affords the compound TEMPO-H. The proposed mechanism suggests that TEMPO-H is then oxidized by O_2 to TEMPO (H_2O formed as by product) to continue the catalytic cycle.

3.3.2.2 Influence of the nature of the solvent on catalytic behaviour

The synthesised metallodendrimers exhibited poor solubility in most common organic solvents. The metallodendrimers **C1** and **C2** showed solubility only in methanol, ethanol and DMF. Other researchers have evaluated the performance of a number of different homogeneous catalysts in different organic solvents. They found that toluene is generally the solvent of choice for the oxidation of alcohols. It has however been reported that the use of DMF as solvent usually gave reasonable activity in catalytic oxidation reactions.[26]

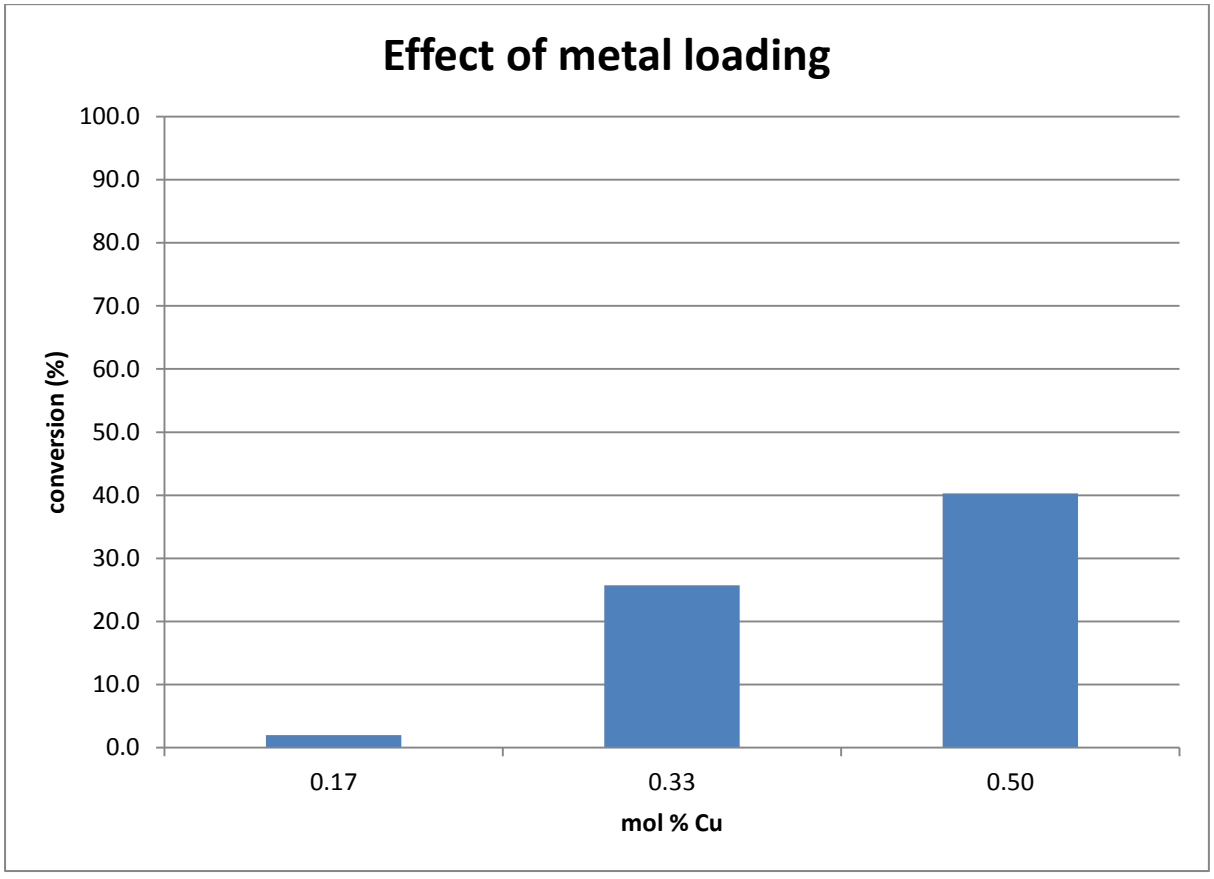
The effects of these two solvents were then tested using the synthesised metallodendrimer catalysts. Both catalysts are insoluble in toluene even at high temperatures. The reaction was therefore performed under “heterogeneous catalytic” conditions by adding solid catalyst to the reaction mixture to form a suspension of catalyst in toluene. After 3 hours the reaction was stopped and the the reaction mixture analysed. A small amount of the product, benzaldehyde had formed. Due to its low solubility the catalyst essentially functioned as a heterogeneous catalyst with very little of the active species dissolved in solution. Low conversion of only 7 % was observed under these conditions.

The toluene was then replaced with DMF in subsequent reactions. The reaction showed much greater conversion of benzyl alcohol to benzaldehyde reaching almost 40% after 3 hours when using **C1** as catalyst precursor. The difference in catalytic activity between the two systems is likely a direct result of the dispersion of the catalyst within the reaction mixture. When using toluene as solvent the catalyst is not fully dissolved and a suspension of the catalyst material in toluene forms. The accessibility of the Cu(II) centers to the substrate molecules is therefore diminished.

This however, is not the case for the DMF system, as the catalyst is completely soluble. The metallodendrimers thus dissolves and discrete metallodendrimer molecules are available for catalysis.

3.3.2.3 Influence of catalyst concentration

The effect of catalyst concentration was then tested. All reactions were performed at 100°C in DMF and under 1 atm of O_2. Figure 3.9 shows the conversions obtained at different Cu(II) loadings. The lowest tested Cu(II) loading of 0.17 mol% showed less than 5% conversion of the substrate. Increasing the loading to 0.33 mol% a much higher conversion of around 25% is observed. Finally at 0.5 mol% loading, the highest conversion of 39 % is observed.



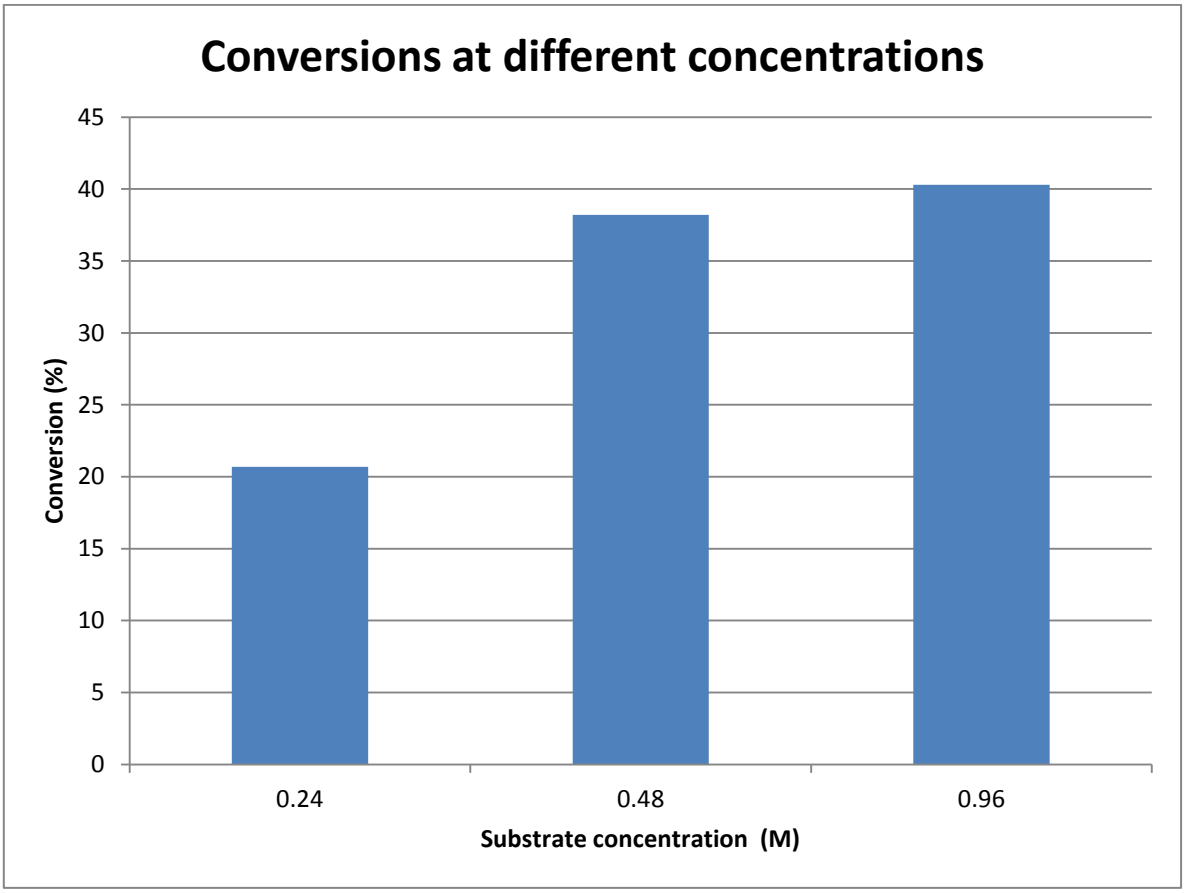
Reaction conditions: 3h, 0.96 mmol benzyl alcohol, 1.3 mol% TEMPO, 1 atm O_2, DMF as solvent 2.02 ml total volume.

Figure 3.9: Effect of catalyst loading on conversion

Additionally, increasing or decreasing the concentration of TEMPO led to lower conversions being observed with almost no conversion (<5%) at 0.7 mol% and 30 % conversion at 2.5 mol%

3.3.2.4 Influence of substrate concentration

The activity of the catalyst **C1** at different substrate concentrations was tested. At low concentrations the reaction showed low catalytic activity as shown in Figure 3.10. At a concentration of 0.96 M the system shows its highest conversion. At higher concentrations the system's catalytic efficiency does not increase further.



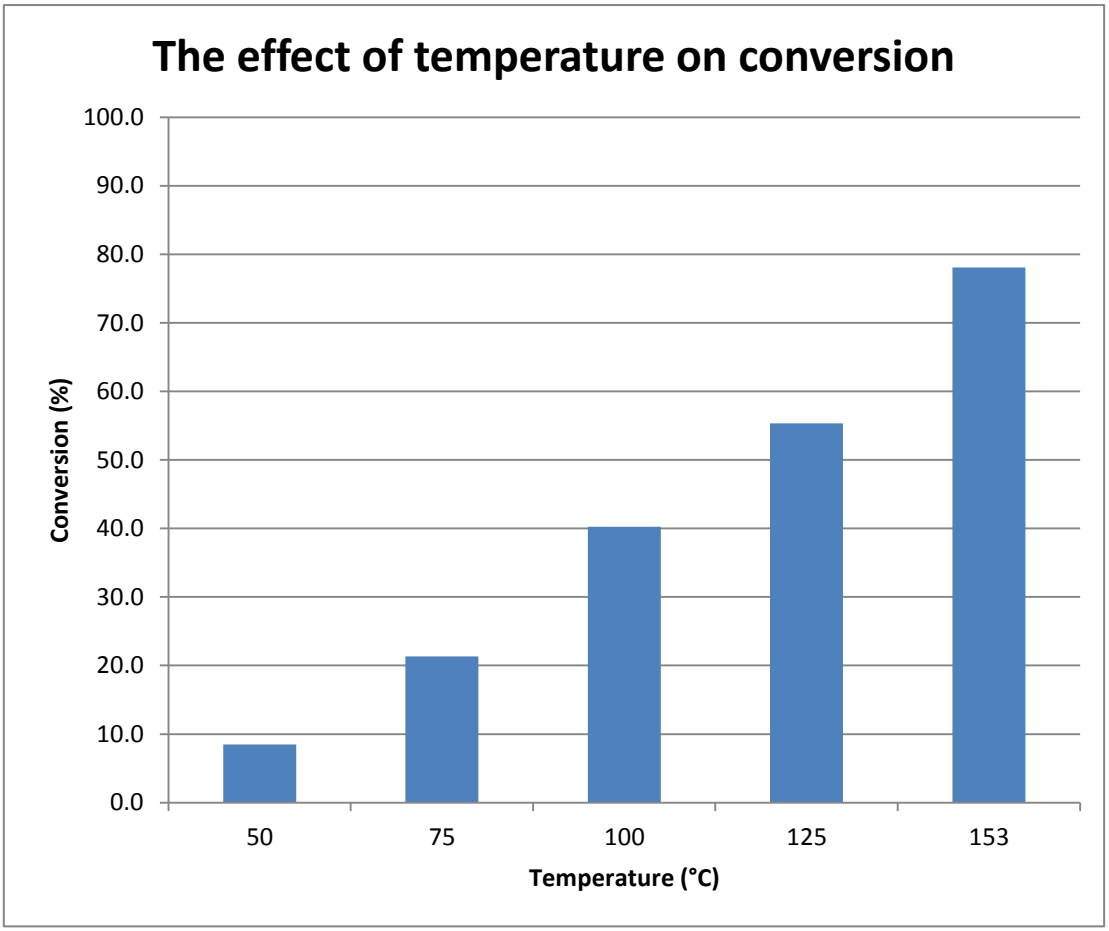
Reaction conditions: 3h, 100°C, 1.3 mol% TEMPO, 0.5 mol% Cu, 1 atm O_2, DMF as solvent 2.02 ml total volume.

Figure 3.10: Effect of substrate concentration on conversion

3.3.2.5 Influence of reaction temperature

The effect of temperature on the catalytic reaction was then tested. All other parameters were kept constant while the temperature was varied. The conditions

employed were: 0.5 mol% Cu, 1.33 mol% TEMPO along with 1 atm O_2. The result of this experiment is displayed in Figure 3.11. At 50°C the catalyst **C1** showed very little activity while increasing the temperature to 75°C leads to almost doubling of the conversion. The conversion of benzyl alcohol to benzaldehyde clearly increases with increasing temperature. The highest conversion is obtained at the boiling point of the solvent, 153°C, where 78% conversion was obtained.



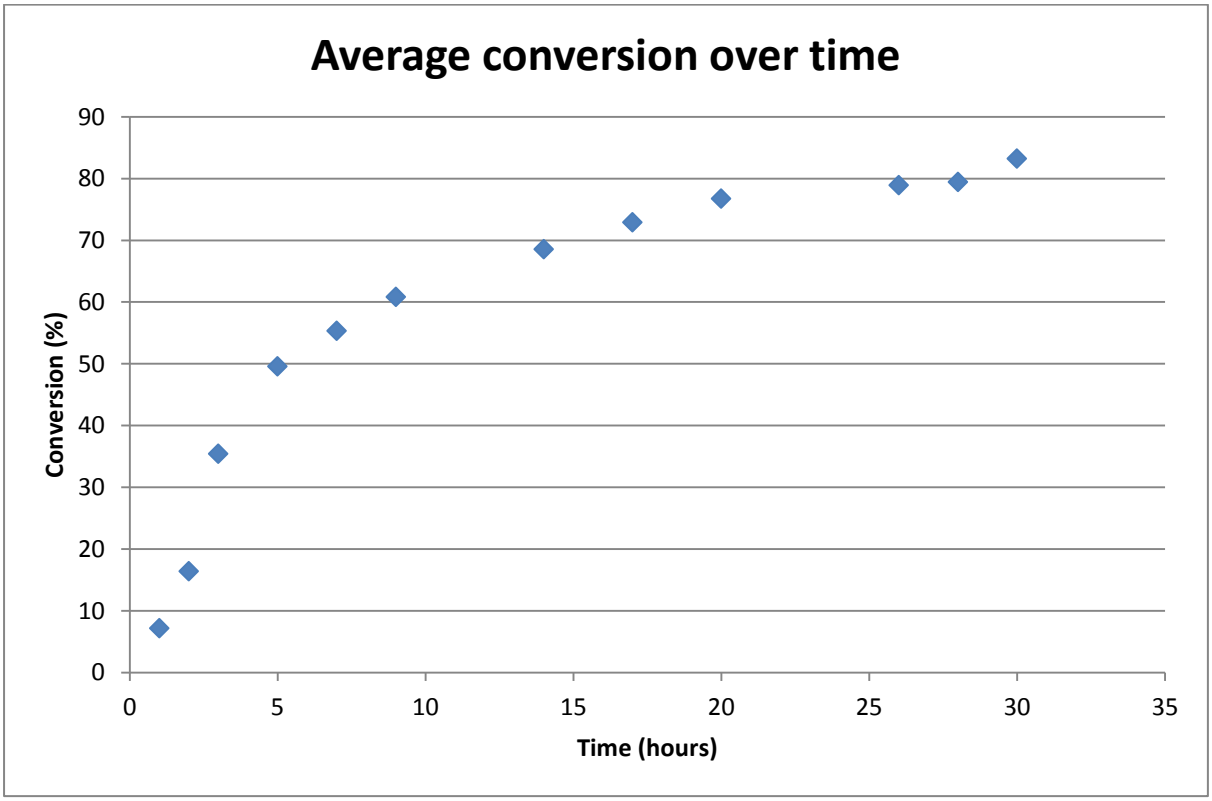
Reaction conditions: 3h, 0.96 mmol benzyl alcohol, 1.3 mol% TEMPO, 0.5 mol% Cu, 1 atm O_2, DMF as solvent 2.02 ml total volume.

Figure 3.11: Effect of temperature on the conversion

3.3.2.6 Influence of time on the reaction

The catalytic reactions were monitored over time, to ascertain the effect of time on the activity of the catalysts. The reaction was also scaled up to allow for multiple samplings. The other reaction parameters were adjusted as well to yield a substrate concentration of 0.48 M, 0.5 mol% Cu as well as 2 mol% TEMPO. The conversion

was monitored over time and the results are shown in Figure 3.12. The conversion initially increases at a rapid rate (hours 0-2). During the next 7 hours the conversion slows down slightly but still increases fairly quickly. After 17 hours the conversion of benzyl alcohol to benzaldehyde slows down remarkably.



Reaction conditions:, 100°C, 1.33 mol% TEMPO, 0.5 mol% Cu, 1 atm O_2, DMF (4.04 ml total volume) and 1.92 mmol substrate

Figure 3.12: Conversion measured over time

The activity of the catalyst was then calculated and expressed as turnover frequency (TOF) and given as mol product formed per mol Cu per hour. These results are shown in Table 3.1. The catalyst exhibited the highest activity after one hour (Table 3.1 entry 1). When the system is operated at 100°C the turnover frequency is 17.7 after one hour. After the first hour the catalyst's activity decreases but stays roughly the same for the next 8 hours. After 9 hours the catalyst's activity starts decreasing quickly again (Table 3.1 entry 6). This is a likely indication of catalyst deactivation taking place. After 28 hours the catalyst's activity has dropped by roughly 60% of its initial value (Table 3.1 entry 11).

When the catalyst **C1** is operated under the optimized conditions (150°C, DMF solvent, 0.5 mol% catalyst, 1.33 mol% TEMPO) much higher TOF's are observed. After 1 hour (entry 12) the TOF is much higher than that observed at 100°C after an hour. As was observed at 100°C (entries 1-11), the TOF starts decreasing with time and rapidly decreased to 30.3 after 3 hours (entry 14).

Table 3.1: Calculated turnover frequencies for C1

Entry	Time (h)	Temp (°C)	TOF
1	1	100	17.7
2	2	100	14.4
3	3	100	10.9
4	5	100	11.3
5	7	100	11.3
6	9	100	11.2
7	14	100	9.1
8	17	100	8.6
9	20	100	7.5
10	26	100	5.6
11	28	100	5.5
12	1	150	40.2
13	2	150	35.7
14	3	150	30.3

Conditions: 0.5 mol% Cu, 1.33 mol% TEMPO, 0.96 M benzyl alcohol (in DMF)

3.3.2.7 The catalytic activity of nickel metallodendrimer **C2**

Choudary *et al* reported a nickel hydrotalcite capable of activating molecular oxygen and subsequently used this catalyst in the catalytic oxidation of alcohols to carbonyls.[32] Their catalyst showed good activity obtaining yields of 98% after 6 hours for the oxidation of 4-nitrobenzyl alcohol.

C2 was therefore also tested as catalyst in the oxidation of benzyl alcohol to benzaldehyde. Unfortunately C2 showed poor activity, yielding conversions similar to that of a system in which TEMPO is used in the absence of catalyst precursor. Yielding conversions < 10% after 3 hours using the conditions optimized for **C1**.

3.4 Conclusions

A range of metallodendrimers based on a cyclam-cored salicylaldimine functionalized dendritic ligand was successfully synthesized and characterized using a range of analytical techniques including FT-IR, UV-Vis and NMR spectroscopy (where appropriate) as well as mass spectrometry, TGA and elemental analysis. The Cu(II) and Ni(II) catalytic systems were then tested as catalysts for the oxidation of benzyl alcohol to benzaldehyde with TEMPO as co-catalyst and at 1 atm O_2. The effect of the different components of the catalytic system was evaluated. Without any catalyst a small amount of conversion takes place due to TEMPO acting as oxidant. However, without TEMPO or O_2 no conversion was observed. These components are crucial to completing the catalytic cycle, as was, found by Sheldon *et al* during their catalytic investigations.[28]

The different reaction parameters, namely the nature of the solvent, the concentration of catalyst as well as the concentration of substrate and finally the reaction temperature were optimized to maximize the conversion of benzyl alcohol to benzaldehyde. The highest conversion was achieved when the system was operated under the conditions: 0.5 mol% Cu, 1.33 mol% TEMPO, 0.96 M substrate in DMF at a temperature of 153°C. The Cu (II) system, **C1**, displayed relatively good catalytic activity achieving its highest TOF of 40.2 after 1 hour. While the Ni(II) system, **C2**, was not very active for the transformation.

3.5 Experimental section

3.5.1 General methods and instrumentation

All chemicals were purchased from Sigma Aldrich and used without any further purification. Solvents used were distilled and dried using the appropriate drying agents and methods prior to use. Catalytic reactions were performed in a Radleys 12-stage carrousel parallel reactor with a gas distribution system. The products from the catalytic reactions were analysed on a Varian 3900 gas chromatograph equipped with a Cyclosil-β (30 m x 0.25 mm x 0.25 μm) column. UV-Vis spectroscopy was performed using a GBC 920 spectrometer. Fourier transform infrared spectroscopy was performed using a Thermo Nicolet Avatar 330 with a Smart Performer Zn/Se

ATR accessory. Mass spectrometry was performed on a Waters Synapt G2 mass spectrometer.

3.5.2 Synthesis and characterization of **C1**

A two necked round bottomed flask (50 ml) was charged with ligand **16** (100 mg, 0.0932 mmol). A solution of copper(II) acetate monohydrate (56.0 mg, 0.279 mmol) in ethanol (10 ml) was added and the mixture refluxed under nitrogen for 24 hours. The mixture was cooled overnight in a freezer and any precipitated material (unreacted ligand) removed by filtration. The filtrate was then concentrated under reduced pressure. Diethyl ether was slowly added until a precipitate forms. The mixture was filtered and the filter dried under vacuum to yield **C1** as a green solid. (Yield, 70%). Mp (DEC) 191-193°C; UV-Vis (λ_{max}) 229, 242, 275, 304, 368 nm; IR (ATR) υ =1617, 1535, 1436, 1395 cm^{-1}; MS (ESI): *m/z* 1258.4 $[M]^+$; E.A. *Anal* Calc. ($C_{62}H_{82}N_{12}O_{12}Cu_3 \circ 10H_2O$) C, 47.79, H, 6.60, N, 10.79, Found: C, 47.03, H, 6.46, N, 10.59.

3.5.3 Synthesis and characterization of **C2**

A two necked round bottomed flask (50ml) is charged with of ligand **16** (100 mg, 0.0932 mmol). A solution of nickel(II) acetate tetrahydrate (70.0 mg, 0.279 mmol) in ethanol was added (10 ml). The mixture was then refluxed for 24 hours under argon. After 24 hours a precipitate had formed. The supernatant was removed with a syringe. The solid was washed by adding ethanol (10 ml) and stirring the mixture for a further hour. The supernatant was removed via syringe. This process was repeated three times. After removing the supernatant the third time the resulting green powder was dried under vacuum to yield **C2** as a brown-green solid. (Yield, 65%). Mp (DEC) 206-209°C; UV Vis (λ_{max}) 224, 240, 264, 370 nm; IR (ATR) υ = 1610, 1538, 1443, 1401 cm^{-1}; MS (ESI) *m/z* 1245 $[M]^+$; E.A. *Anal*. Calc. ($C_{62}H_{82}N_{12}O_{12}Ni_3 \circ 8H_2O$) C, 49.39, H, 6.55, N, 11.15, Found: C, 48.76, H, 6.16, N, 10.85.

3.5.4 Synthesis and characterization of **C3**

16 (0.100 g, 0.0932 mmol) and zinc(II) acetate dihydrate (61.2 mg, 0.279 mmol) were dissolved in ethanol (10 ml) and the reaction mixture refluxed for 24 hours under nitrogen. The reaction mixture was then cooled in a freezer and filtered. The filtrate was concentrated under reduced pressure. Diethyl ether was then added to form a precipitate. The precipitate was filtered and dried under vacuum to yield **C3** as a highly hygroscopic cream coloured solid (yield, 70%). IR (ATR) υ =1618, 1535cm^{-1}; ^{1}H NMR (600 MHz, DMSO-d_6) δ_H: 1.38 (t, 4H, -N-CH$_2$-C**H$_2$**-CH$_2$-N-), 2.17 (2H,N-C**H$_2$**-), 2.31-2.67 (m, 24H, -C**H$_2$**-N-, -N-CH$_2$-C**H$_2$**-CONH-), 3.19.0-3.72 (m, 16H, =N-CH$_2$-C**H$_2$**-CONH-, =N-C**H$_2$**-CH$_2$-CONH-) 6.44 (br, 4H, **H**-Ar), 6.55 (br, 4H, **H**-Ar), 7.15 ppm (s, 8H, **H**-Ar), 8.12-8.40 ppm (br, 4H, -**H**C=N-); ^{13}C NMR (600 MHz, DMSO δ_6) δ_c : 22.5 (-N-CH$_2$-**C**H$_2$-CH$_2$-N-,), 33.0 (-N-CH$_2$-**C**H$_2$-CONH-CH$_2$-), 39.9 (-CH$_2$CONH-**C**H$_2$-), 48.6 (-N-**C**H$_2$-**C**H$_2$-N-), 49.7 (-N-**C**H$_2$-CH$_2$-**C**H$_2$-N-), 51.0 (-N-**C**H$_2$-CH$_2$-CONH-), 59.1 (-**C**H$_2$-C=N), 112.9 (Ar), 118.4 (Ar), 122.3 (Ar), 134.0 (Ar), 136.0 (Ar), 170.3 (Ar-OH), 171.6 ppm (-NH**C**O-) 175.2 (-**C**=N-)

3.5.5 Representative example of a typical catalytic test reaction

The catalytic oxidation of benzyl alcohol to benzaldehyde, employing the conditions used in section 3.3.4, is fully discussed as a representative example of a typical benzyl alcohol oxidation reaction.

C1 is added from a stock solution (0.0030 M in DMF) to yield a solution containing 0.5 mol% copper (relative to 0.96 mmol benzyl alchohol). The co-catalyst (1.33 mol% relative to 0.96 mmol benzyl alcohol) is then also added from a stock solution (0.015 M in DMF). Additional solvent is added to make up a 1.92 ml reaction volume. The reaction mixture is then saturated with oxygen by bubbling O_2 through the solution for 1 minute. The resulting mixture is then heated under 1 atm of O_2 until the desired temperature (100°C) is reached. The substrate, benzyl alcohol, (0.96 mmol, 0.1 ml) is then added through a septum. The reaction is stirred at 100°C for 3 hours under 1 atm of O_2. After 3 hours the reaction tube is cooled in an ice bath for 5 minutes. A sample of 0.1 ml is then taken from the reaction solution and diluted with 0.8 ml

methanol, this sample was then analysed by GC using *p*-xylene (0.1ml) as internal standard.

3.6 References

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CHAPTER 4: CHAPTER SUMMARIES, CONCLUDING REMARKS AND FUTURE WORK

4.1 Summmary of content discussed by chapter

The historical origins of dendrimers and dendrimer architecture are examined in **Chapter 1**. Mention is made of the first examples of dendrimers synthesized by the groups of Vögtle, Tomalia and Newcomb *et al*. The different synthetic approaches employed in synthetic dendrimer chemistry (namely convergent and divergent methods) are then discussed along with the advantages and disadvantages of these methodologies.

The potential applications of dendrimers are then examined by highlighting several examples where dendrimers were successfully used. It is shown that dendrimers are successfully applied in biomedical applications, as drug delivery vectors or as synthetic proteins. Metallodendrimers have also proven useful as recyclable catalysts utilizing either transition metal complexes or metal nano particles. Dendritic effects are sometimes observed in these systems. Examples of both positive effects such as increased selectivity as well as negative dendritic effects such as decreased activity are reported for the different systems reviewed.

Macrocyclic ligands are then discussed. The origin of this class of ligands is reviewed- from the synthetic work of Ray, who synthesised the first macrocycles, to the pioneering work of Pederson who synthesized the first macrocycle complexes. The applications of macrocycles are then discussed and include their use in the field of metal extraction, their use in the treatment of HIV/Aids and finally their use in the field of catalysis.

Chapter 1 concludes with a short review of reported dendrimer-macrocycle conjugates and the proposed aims of the project namely the synthesis of dendrimer-

macrocycle conjugates and the use of these materials as ligands for the preparation of multinuclear complexes. An additional aim was to evaluate some of these dendritic complexes as catalyst precursors in the oxidation of alcohols.

Chapter 2 deals with a discussion on the synthesis of a number of proposed dendrimer-macrocycle conjugates. The first proposed dendrimer requires a mono-N functionalized macrocycle. Several methods to synthesise such a compound were explored and employed to varying degrees of success.

Attempts at synthesizing a dendritic ligand based on peripheral cyclam units utilizing a click reaction are discussed. The relevant functional groups (azide and alkyne) are incorporated onto a dendrimer core and what will become the dendrimer periphery.

Finally the synthesis of dendritic ligand with a macrocyclic core is discussed. Dendritic arms are synthesised utilizing the synthetic protocols often employed for PAMAM dendrimers, namely iterative sequences of Michael addition (with methyl acrylate) followed by amidation reactions (with ethylene diamine). Subsequent reaction with salicylaldehyde yielded a cyclam cored dendrimer with salicylaldimine peripheries.

The synthesis and full characterization of metallodendrimers (using Cu, Ni and Zn salts) and their application in the catalytic oxidation of alcohols is described in **Chapter 3**. Reported catalytic oxidation systems as well as their advantages and disadvantages are briefly reviewed. Two mechanisms, proposed by Semmelhack *et al* and Sheldon *et al* respectively, for a Cu/TEMPO catalytic system are discussed. Several desirable properties for a successful catalytic oxidation system are also identified. The synthesised Cu and Ni metallodendrimers were then tested as catalysts in the catalytic oxidation of alcohols along with the co-catalyst, TEMPO. Several reaction parameters are each optimized, in turn, to maximize catalytic efficiency. Using the optimized system the TON and TOF of the system were determined. It is observed that the Cu metallodendrimer **C1** is a relatively active alcohol oxidation catalyst achieving 78% conversion after 3 hours when operated under the optimized conditions (0.5 mol% Cu, 153°C, 1.33 mol% TEMPO, 1 Atm O_2 and DMF as solvent). The Ni metallodendrimer **C2** on the other hand, achieves rather low conversions (< 5%) under the optimized conditions after 3 hours.

4.2 Conclusions

The aims of the project, as previously stated, were the synthesis of macrocycle-dendrimer conjugates, as well as the complexation of such a ligand to a range of transition metal salts. The synthesis of several such systems and their corresponding metallodendrimers were attempted.

The synthesis of a mono-N-functionalized macrocycle is required for the proposed synthesis of a DAB cored dendrimer with macrocycle peripheries. A linker molecule was successfully synthesised 4-(bromomethyl) benzaldehyde. Subsequently a mono-N-functionalized macrocycle (**8**) was synthesized. Reaction with the DAB PPI core was followed by FT-IR and showed the formation of the C=N moiety however subsequent reaction with TFA/DCM to remove Boc protecting groups led to the hydrolysis of the imine groups. Attempts to remove the Boc protecting groups before reaction with the DAB PPI core however lead to unacceptably low yields.

Synthesis of a Boc-protected click dendrimer was then accomplished, however when attempting to deprotect the compound a complex mixture of products was obtained. The product range likely consists of variants of the click dendrimer with 1 or more cyclam amines that are still Boc protected along with some fully de-protected dendrimers.

A macrocycle cored dendrimer was successfully synthesised. The synthesised dendritic ligand was characterized by FT-IR, ^{1}H and ^{13}C NMR as well as mass spectrometry. The relevant C=N stretch as well as the the relevant imine proton and carbon resonances were observed in FT-IR, ^{1}H and ^{13}C NMR respectively. Mass spectrometry data showed the molecular ion $[M+H]^{+}$.

Upon successful synthesis of **16** the metallodendrimers **C1**-**C3** were synthesized. The dendritic complexes **C1** and **C2** had three metal centres per dendritic ligand, with coordination occurring through the salicylaldimine peripheries and the cyclam core. The complex **C3** however does not coordinate through the cyclam moiety. These complexes were characterized by FT-IR, UV-Vis spectroscopy mass spectrometry, elemental analysis, TGA and magnetic susceptibility measurements (where appropriate). The FT-IR spectra showed the expected shifts in the imine stretch upon coordination. UV-Vis spectra showed the MLCT bands (where

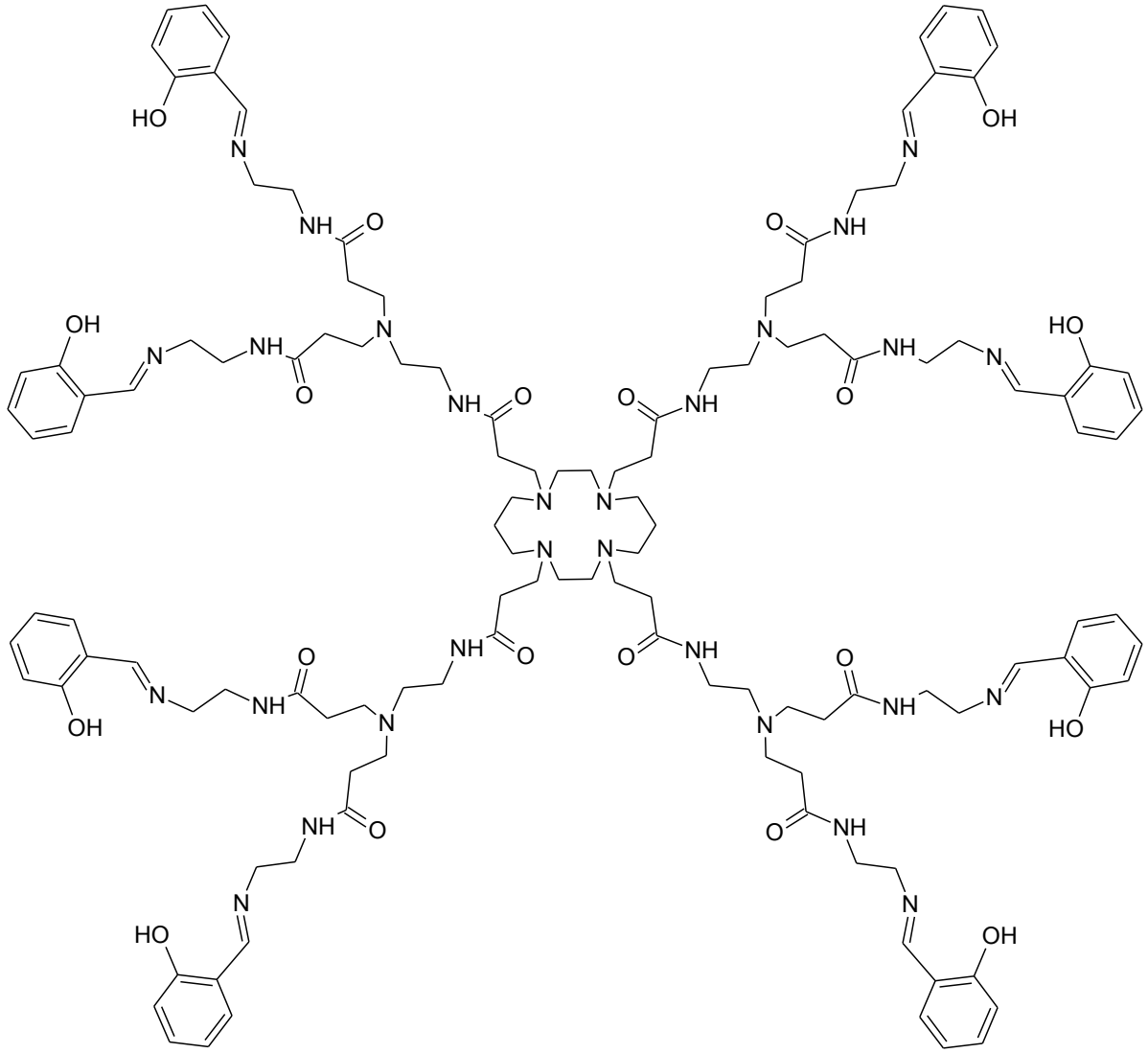
appropriate) expected for the complexes **C1** and **C2**. The molecular ion is observed for both **C1** and **C2** under ESI-MS conditions. Elemental analysis results indicated that water was most likely present in both **C1** and **C2**, this agrees with the observation that these complexes appear to be hygroscopic. From the characterization data it was concluded that the synthesis of **C1**-**C3**, was performed successfully.

The metallodendrimers **C1** and **C2** were tested as catalysts for the catalytic oxidation of benzyl alcohol. The Cu metallodendrimer **C1**, showed promise as an oxidation catalyst. **C1** achieved fairly high conversion when operating under the optimized conditions. The catalytic activity was highest when DMF was used as solvent; this is due to the poor solubility of the metallodendrimers in common organic solvents. The highest conversion was achieved when working at 0.5 mol% Cu catalyst while it was determined that a minimum of 1.33 mol% TEMPO was required for maximum activity. Increasing the co-catalyst loading further did not appreciably increase the activity of the catalytic system. The highest conversion was obtained when the system was operated at 153°C the boiling point of DMF, in all cases lower temperatures showed lower conversions for these test reactions. It is observed that catalyst deactivation takes place over time with the TON's decreasing rapidly after 3 hours (or even 1 hour at the optimized conditions). The metallodendrimer **C2** however performed poorly as an alcohol oxidation catalyst achieving less than 10% conversion after 3 hours under the optimized conditions. It is possible that the Ni catalyst does not easily undergo the necessary redox reactions for the process to be catalytic. As was shown in the catalytic cycle of Sheldon *et al* (Scheme 3.4) Cu^{+} is an important intermediate during the reaction. The standard reduction potentials for Cu^{2+} and Ni^{2+} show that Cu^{2+} easily reduces to Cu^{+} while the formation of Ni^{+} is thermodynamically unfavourable, as was reported by others.[1,2]

4.3 Suggestions for future work

The metallodendrimer **C2**, along with co-catalyst TEMPO, has proven relatively active as an oxidation catalyst. The generation of the dendrimer can be increased to the second and the third generation by applying an iterative sequence of Michael addition reactions (reaction with methyl acrylate) followed by amidations (reaction

with ethylene diamine) reactions. An example of such a proposed second generation dendrimer is shown in Figure 4.1.



FW1

Figure 4.1: A proposed 2nd generation dendrimer based on a cyclam core

Ligand **FW1** can then be used to prepare higher generation metallodendrimers. As previously mentioned positive and negative dendrimer effects are sometimes observed as the generation of the dendrimer increases. Such a system could likely have interesting catalytic properties.

A number of desirable properties for successful oxidation catalysts are mentioned in **Chapter 3**. The system should preferably be recyclable; therefore the recyclability of the dendritic catalysts should be tested. The catalysts can be removed from the product stream using ultra filtration and their activity in subsequent catalytic runs be tested. Potential leaching of metal ions from the metallodendrimer can be tested by analysing the product stream with ICP analysis.

The use of environmentally friendly oxidants is also identified as particularly desirable for a catalytic oxidation system. The use of atmospheric air as opposed to baseline O_2 as oxidant should be tested as this would be economically advantageous. Hydrogen peroxide (H_2O_2) is also regarded as an environmentally friendly oxidant. It would be interesting to evaluate the activity of the catalytic system using H_2O_2 as oxidant.

4.4 References

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